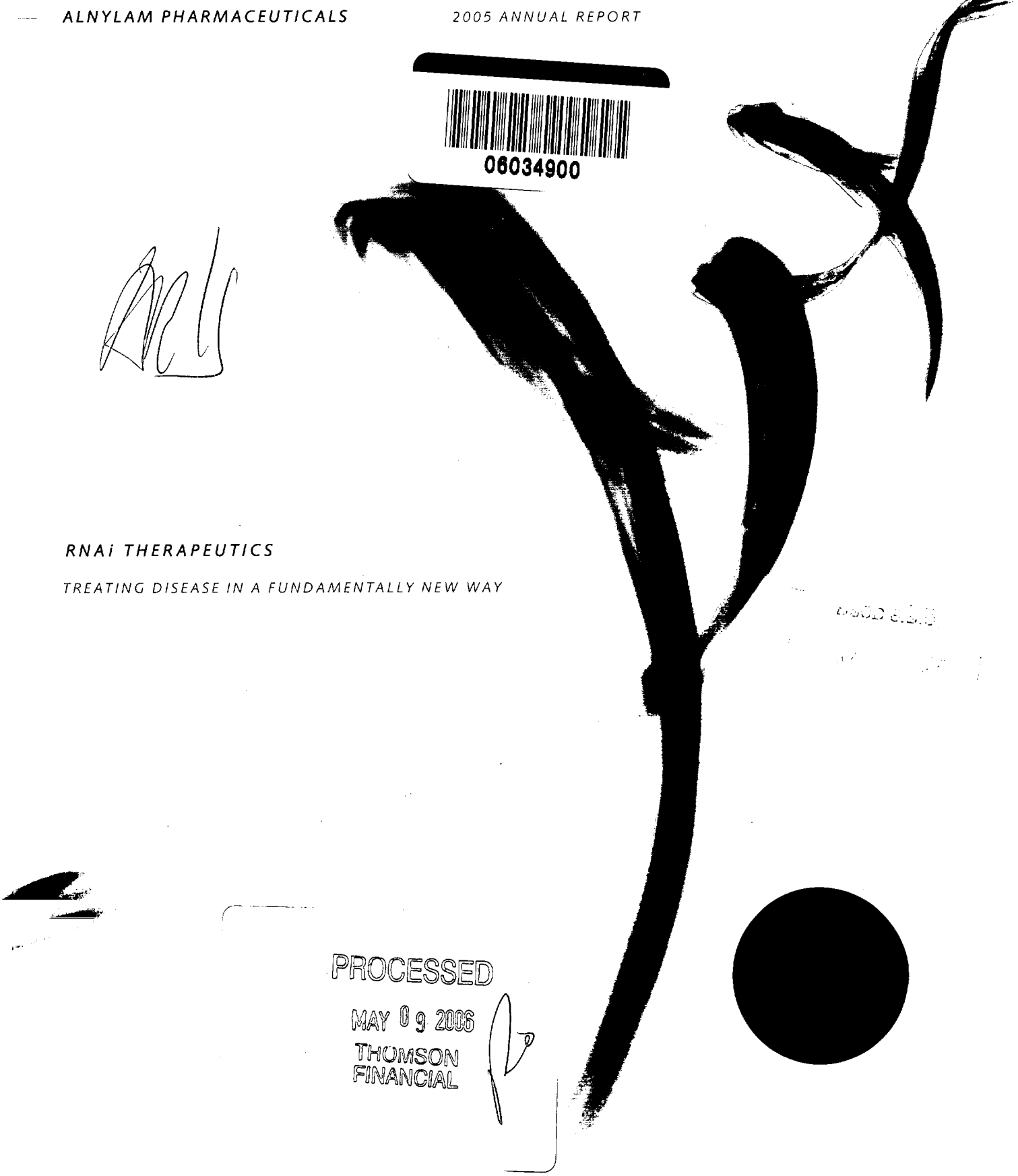
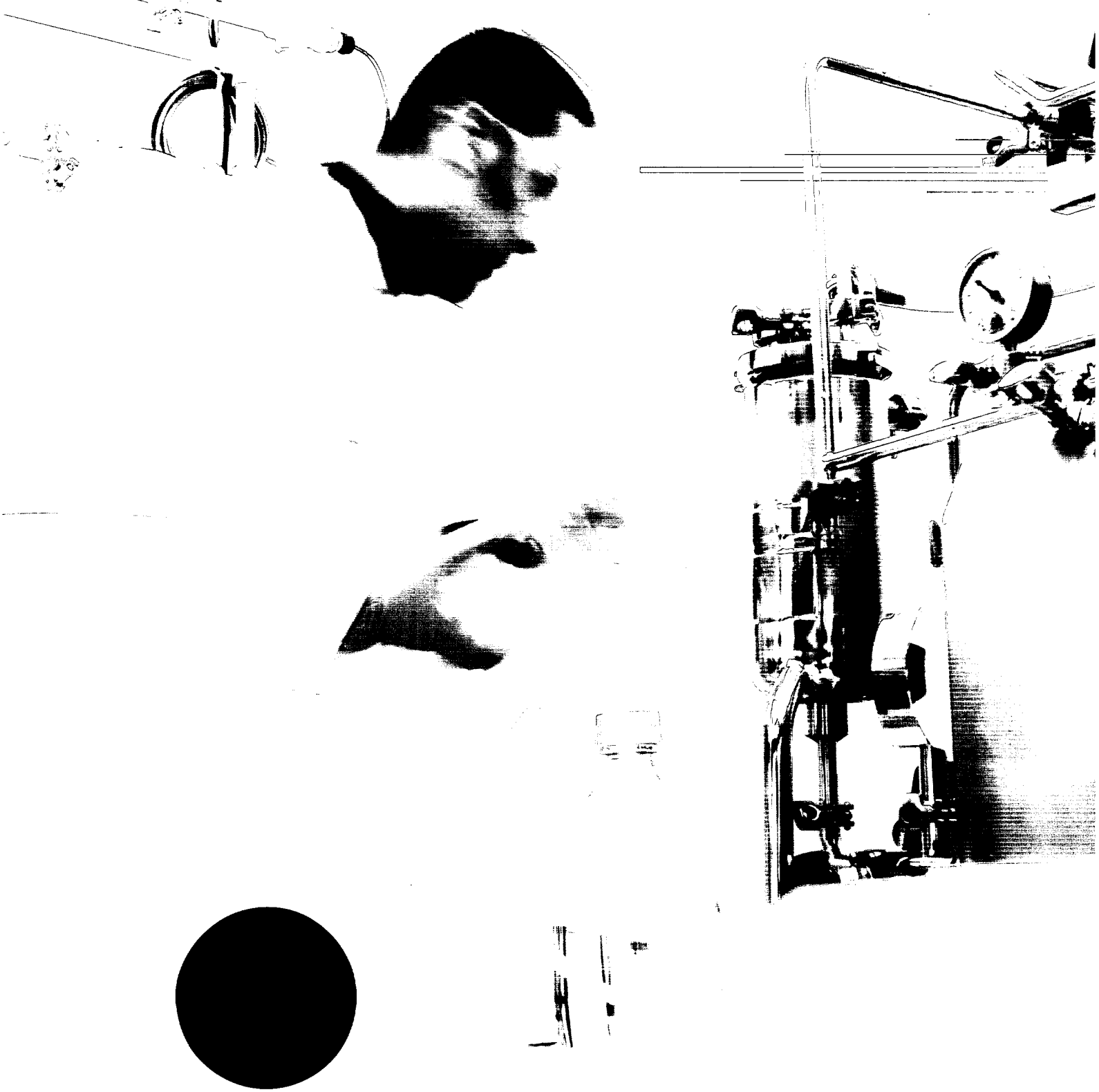


RNAi THERAPEUTICS

TREATING DISEASE IN A FUNDAMENTALLY NEW WAY



VISION

HARNESSING A REVOLUTION IN BIOLOGY FOR HUMAN HEALTH®

MISSION

BUILD A LEADING PRODUCT COMPANY FOUNDED ON RNAi

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

☑ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2005

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File Number 000-50743

ALNYLAM PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**77-0602661**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification No.)*

300 Third Street, Cambridge, MA 02142

(Address of principal executive offices) (Zip Code)

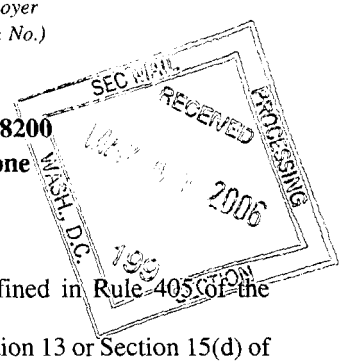
Registrant's telephone number, including area code: (617) 551-8200

Securities registered pursuant to Section 12(b) of the Act: None

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, $0.01 par value per share

(Title of Class)



Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☑

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☑

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☑ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☑

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act (Check one):

Large accelerated filer ☐ Accelerated filer ☑ Non-accelerated filer ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☑

The aggregate market value of the voting Common Stock held by non-affiliates of the registrant, based on the last sale price of the registrant's Common Stock at the close of business on June 30, 2005, was $123,617,872.

As of February 28, 2006, the registrant had 31,921,314 shares of Common Stock, $0.01 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Items 10, 11, 12, 13 and 14 of Part III (except for information required with respect to our executive officers, which is set forth under "Part I, Item 1 — Business — Executive Officers of the Registrant") and the information required by Item 5 relating our equity compensation plans have been omitted from this report, as we expect to file with the Securities and Exchange Commission, not later than 120 days after the close of our fiscal year ended December 31, 2005, a definitive proxy statement for our annual meeting of stockholders. The information required by Items 10, 11, 12, 13 and 14 of Part III and the information required by Item 5 relating to our equity compensation plans, which will appear in our definitive proxy statement, is incorporated by reference into this report.

ALNYLAM PHARMACEUTICALS, INC.
ANNUAL REPORT ON FORM 10-K
For the Year Ended December 31, 2005

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This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, that involve risks and uncertainties. All statements other than statements relating to historical matters (including statements to the effect that we "believe," "expect," "anticipate," "plan," "target" and similar expressions) should be considered forward-looking statements. Our actual results could differ materially from those discussed in the forward-looking statements as a result of a number of important factors, including the factors discussed in this section and elsewhere in this Annual Report on Form 10-K, including those discussed in Item 1A of this report under the heading "Risk Factors," and the risks discussed in our other filings with the Securities and Exchange Commission. Readers are cautioned not to place undue reliance on these forward-looking statements, which reflect management's analysis, judgment, belief or expectation only as of the date hereof. We assume no obligation to update these forward-looking statements to reflect events or circumstances that arise after the date hereof.

PART I

ITEM 1. BUSINESS

Overview

We are a biopharmaceutical company seeking to develop and commercialize new drugs that work through a recently discovered system in cells known as RNA interference, or RNAi. We believe that drugs that work through RNAi, or RNAi therapeutics, have the potential to become a new major class of drugs, like small molecule, protein and antibody drugs. Because of their mechanism of action, RNAi therapeutics could represent a fundamentally new way of treating disease and, therefore, be used to address a broad range of unmet medical needs.

Our initial drug development programs are focused on products we call Direct RNAi™ therapeutics, because they will be administered directly to diseased parts of the body. In parallel, we are establishing capabilities for the development of products we call Systemic RNAi™ therapeutics, because they will travel through the blood stream to reach diseased parts of the body. We believe there are multiple opportunities for both Direct RNAi and Systemic RNAi therapeutics.

Our most advanced product candidate is ALN-RSV01, a Direct RNAi therapeutic for the treatment of lung infections caused by respiratory syncytial virus, or RSV. We initiated human clinical trials of ALN-RSV01 in December 2005. The next product candidate we expect to advance into clinical development will be for another lung infection, influenza, or flu. We expect to submit an investigational new drug application, or IND, for an RNAi therapeutic for pandemic flu as early as the end of 2006. Our program to develop an RNAi therapeutic for pandemic flu is being conducted in collaboration with Novartis Institutes for Biomedical Research, Inc., an affiliate of Novartis Pharma AG, who with Novartis Pharma AG, we refer to as Novartis.

We also have discovery programs to develop Direct RNAi therapeutics for the treatment of the genetic respiratory disease known as cystic fibrosis and nervous system disorders such as spinal cord injury, Parkinson's disease, Huntington's disease and neuropathic pain. Additionally, we have discovery programs in ocular diseases such as age-related macular degeneration and several other diseases that are the subject of collaborations with Merck & Co., Inc., or Merck, and Novartis.

Our main business strategy is to develop and commercialize a pipeline of proprietary RNAi therapeutic products and, in parallel, to form alliances with pharmaceutical companies to develop and commercialize a pipeline of partnered RNAi therapeutics. To date, we have formed such alliances with Merck, Novartis and Medtronic, Inc., or Medtronic.

RNA Interference

RNAi is a recently discovered mechanism that occurs naturally within cells and selectively silences the activity of specific genes. Genes provide cells with instructions for producing proteins. Proteins perform many of the vital functions of the cell and of the human body. Although the roles they play are generally beneficial, in certain circumstances, proteins can be harmful. Many human diseases are caused by the inappropriate behavior of proteins. A particular protein may, for example, be present in too great a quantity, be too active or appear in the wrong place or

at the wrong time. In these circumstances, the ability to stop or reduce production of the protein by selectively silencing the gene that directs its synthesis could be very beneficial for the treatment of the disease.

Beginning in 1999, our scientific founders described and provided evidence that the RNAi mechanism occurs in mammalian cells and that its immediate trigger is a type of molecule known as small interfering RNA, or siRNA. They showed that laboratory-synthesized siRNAs could be introduced into the cell and suppress production of specific target proteins. Because it is possible, in theory, to design and synthesize siRNAs specific for any gene of interest, we believe that RNAi therapeutics have the potential to become a broad new class of drugs.

How RNA interference Works

RNA is a crucial intermediary in the process by which the cell uses inherited genetic information. This information is passed from one generation to the next in the form of genes, which are made of a substance known as deoxyribonucleic acid, or DNA. Generally, each gene contains the instructions that tell the cell how to make one specific protein. These instructions are in a coded form. The code is based on the four different chemical building blocks from which DNA is made, usually designated by the first letters of their chemical names, A, C, G and T. It is the sequence in which these building blocks, or bases, occur in a gene that tells the cell what protein to make. Most gene sequences are thousands of bases long, and the variety possible in such long sequences allows the cell to produce a large number of different proteins.

One very important property of DNA is that it is double-stranded, consisting of two separate strands intertwined around each other in a double helix. The two strands are held together by base pairs that form between bases on the opposite strands. Strict rules govern the formation of these base pairs: an A on one strand can pair with a T on the other, and a G can pair with a C, but no other pairings are allowed. The double-stranded nature of DNA and the strict rules governing base-pairing are fundamental to ensuring that genetic information is copied accurately when it is handed down from one generation to the next.

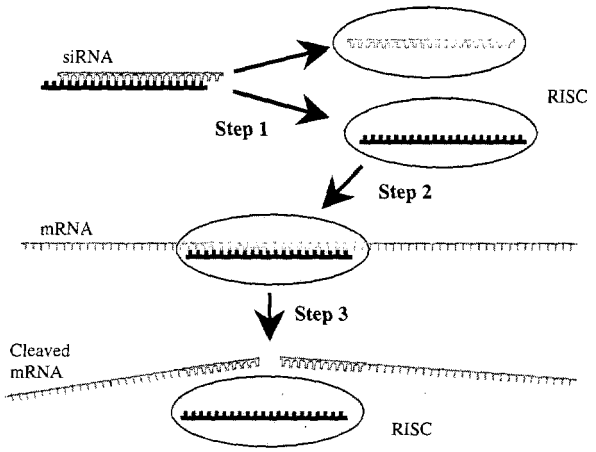
Base-pairing rules are also fundamental to the process by which the cell uses, or expresses, genetic information to make a protein. To initiate this process, the cell makes a working copy of the gene that encodes the protein. This working copy is made not of DNA but of a closely related substance called ribonucleic acid, or RNA. The working copy is known as messenger RNA, or mRNA. Unlike DNA, mRNA has only one strand. However, the application of base-pairing rules during synthesis of this strand ensures that the sequence of bases in mRNA accurately reflects the base sequence, and thus the genetic information, in the gene being copied. This mRNA then associates with the cell's protein synthesis machinery, where it directs synthesis of a protein in such a way that the structure of the protein is directly determined by the sequence of bases in the mRNA, and thus in the gene. The protein specified by a particular gene or mRNA is said to be encoded by that gene or mRNA. When this protein is made, the gene is said to be active or expressed.

Although many RNA molecules, like mRNA, are single-stranded, RNA is capable of forming double-stranded molecules analogous to those formed by DNA. When it does so, base-pairing rules apply. As a result, only RNA molecules with complementary sequences can form double-stranded structures. Generally, every base on one strand has to line up with its permitted base-pair partner on the other strand, otherwise the double-stranded structure will be unstable.

Double-stranded RNA, or dsRNA, is crucial to the phenomenon of RNAi. A particular type of dsRNA interferes with the activity of specific genes by triggering the breakdown of mRNAs copied from these genes, preventing production of the proteins they encode. Selection of mRNAs for breakdown is driven by base-pairing between the target mRNAs and the separated strands of the dsRNA. Thus, the mRNAs selected for breakdown are those which contain base sequences identical to base sequences in one strand of the dsRNA. As a result, RNAi leads to selective silencing of specific genes with relatively little impact on other genes whose mRNAs do not share base sequences with the dsRNA.

In nature, the cell initiates RNAi by cutting longer dsRNAs into smaller dsRNA pieces that have 25 or fewer base pairs. These shorter dsRNAs are known as small interfering RNAs, or siRNAs. siRNAs are double-stranded along most of their length but have unpaired bases, or overhangs, at each end, which are important for their activity. siRNAs are the molecules that actually trigger RNA interference. They do so by a process that has three main steps as shown in the figure below.

Figure 1: RNA interference as triggered by an siRNA



Step 1. siRNAs associate with several proteins to form an assembly known as the RNA-induced silencing complex, or RISC. The two strands of the siRNA become separated as the RISC is formed, so that RISC contains an unpaired single-stranded RNA.

Step 2. The RISC then looks for mRNA molecules that contain base sequences complementary to the single-stranded RNA it contains — that is, sequences within the mRNA whose bases can pair up exactly, using base-pairing rules, with the bases in the single-stranded RNA.

Step 3. Once this pairing occurs, the RISC complex cuts the mRNA into two separate pieces at the base-paired region, destroying its ability to direct protein synthesis. The RISC complex is then available to cut additional mRNA molecules that contain the appropriate base sequence.

Repetitive cycles through steps two and three lead to catalytic degradation of mRNAs that contain a sequence complementary to the siRNA strand in the RISC. The ability of each RISC complex to cut multiple mRNA molecules consecutively in a catalytic manner is one of the reasons why we believe RNAi will be effective at silencing gene activity.

Opportunity for Therapeutics Based on RNAi

In May 2001, one of our scientific founders published the first scientific paper demonstrating that the siRNAs required to trigger RNA interference need not be generated inside the cell. Instead, siRNAs can be synthesized in the laboratory using chemical or biochemical methods and introduced into cells to silence the activity of a specific gene. As a result of the human genome project, complete base sequences are available for most human genes. With the sophisticated bioinformatics tools that were developed in conjunction with the genome project, it is possible to scan through the gene that encodes a particular protein and select base sequences that are of the appropriate length for siRNAs and unique to that gene. Several siRNAs targeted to the gene of interest can then be synthesized. Each synthesized siRNA will contain a sequence capable of base-pairing exactly with a short stretch of the sequence of the mRNA copied from the target gene. The synthetic siRNAs can then be tested to determine whether they silence the activity of this gene and suppress the synthesis of the protein it encodes.

The use of siRNAs has been broadly adopted by academic and industrial researchers for the fundamental study of the function of genes. Important information about the function of a gene can often be deduced by suppressing,.or

knocking-down, its activity and examining the effect this has on the behavior of a cell or animal. There are now many examples in which such suppression of gene activity has been achieved, in whole or in part, using synthetic siRNAs. In just a few years after siRNAs were discovered, they have become the tools of choice for the selective knock-down of gene function by research scientists, and have largely displaced other methods previously used for this purpose. Reflecting this, siRNAs are a growing portion of the market for research reagents and related products and services.

One important application of such knock-down studies is to confirm the role of a particular gene or protein in a disease, a process often referred to as target identification or target validation. If silencing a gene with an siRNA leads to improvements in disease symptoms in an experimental disease model, this implies that the target gene or protein plays an important role in the disease. It also implies that the siRNA that suppresses the gene in the model system may be a useful starting point for the development of a drug. We believe that it will be possible to develop these siRNAs into potent and specific drugs.

Broad Potential of siRNAs as Therapeutics

The success of siRNAs in silencing gene activity in experimental systems suggests that siRNAs could potentially be developed into a broad class of human therapeutics. We believe this new class of drugs has the potential to become a major class of drugs because RNAi therapeutics could offer the following benefits:

- **Ability to treat a broad range of diseases.** Given the availability of the base sequence of the entire human genome, it could be possible, in theory, to design siRNAs to suppress the production of virtually any human protein whose presence or activity causes disease. This suggests that RNAi therapeutics could potentially be used to treat a broad range of diseases.

- **Ability to target proteins that cannot be targeted effectively by existing drug classes.** Many proteins that play important roles in disease cannot be targeted effectively with small molecules or with therapeutic proteins such as monoclonal antibodies. These proteins are commonly referred to as non-druggable targets. In the case of small molecule drugs, many proteins are non-druggable because it has proved difficult to synthesize drug candidates with appropriate specificity, potency and safety. In the case of protein drugs, the range of available targets is limited to targets on the surface of or outside the cell. These limitations on small molecule and protein drugs should not apply to siRNAs, which, in theory, can be synthesized to target any gene in the genome. Therefore, we believe RNAi therapeutics will be able to target proteins that small molecule and protein drugs cannot currently target.

- **Inherently potent mechanism of action.** One molecule of siRNA could potentially do the work of thousands of molecules of conventional drugs. With conventional drugs, one drug molecule is typically required for every protein molecule whose activity needs to be blocked. Accordingly, to block several thousand protein molecules, several thousand drug molecules are required. In contrast, a single siRNA molecule can potentially block the synthesis of many protein molecules. This is because each siRNA within a RISC complex can trigger destruction of multiple mRNA molecules, each of which could otherwise direct the synthesis of many protein molecules. This inherent potency of the RNAi mechanism suggests a potentially high degree of potency for RNAi therapeutics.

- **Simplified discovery of drug candidates.** Identification of small molecule and protein drug candidates typically requires screening of a large number of potential candidates to find prospective leads. These leads must then undergo significant optimization in order to become drug candidates. Particularly in the case of small molecule drug candidates, the optimization procedure can be very challenging, and has to be almost entirely repeated for each candidate. Identification of siRNA drug candidates has the potential to be much simpler and take considerably less time because, in theory, it will involve relatively standard processes that can be applied in a similar fashion to many successive product candidates.

For these potential benefits of siRNA drugs to be realized, it will be necessary to create chemically synthesized siRNAs that are potent, specific, stable and safe and also capable of reaching the appropriate tissues and cells. The incorporation of such properties into siRNAs is the focus of our product platform. We have reported on our advances

in developing siRNAs as potential drugs in a number of peer-reviewed publications and meetings, including a publication by Alnylam scientists in the journal *Nature*.

Our Business Strategy

Our business strategy is to develop and commercialize a pipeline of *proprietary* RNAi therapeutic products and, in parallel, to form alliances with pharmaceutical companies to develop and commercialize a pipeline of *partnered* RNAi therapeutic products. For our proprietary RNAi therapeutic products, our aim is to develop these products to later stages of clinical development and to commercialize them on our own or through alliances formed at these later stages. For our partnered RNAi therapeutic products, to date, we have formed five discovery and development alliances with three separate companies: Merck, Medtronic and Novartis. Two of these alliances are with Merck, one focused on RNAi technology and RNAi therapeutics directed against Merck proprietary targets, the other focused on RNAi therapeutics for eye diseases. In these Merck alliances, we retain a major role in development and commercialization and a significant financial interest in each product. Our collaboration with Medtronic is focused on the development of novel drug-device products incorporating RNAi therapeutics to treat diseases caused by degeneration of the nervous system. We have two alliances with Novartis. The first of our Novartis alliances, formed in September 2005, is for the discovery, development and commercialization of RNAi therapeutics for a significant but defined number of targets in the Novartis research portfolio. In this alliance, we are eligible to receive substantial early funding in addition to future milestone and royalty payments. We are also eligible to receive additional payments if Novartis exercises a non-exclusive option to integrate our RNAi therapeutics platform into its internal efforts, in which case we would be eligible to receive future milestones and royalties on products resulting from those efforts. Our second alliance with Novartis, formed in February 2006, is for the discovery and development of RNAi therapeutics for pandemic flu. In this alliance, we and Novartis will jointly develop RNAi therapeutics for pandemic flu in the United States, with Novartis leading development outside the United States. Novartis will also lead commercialization efforts world-wide, with Alnylam actively involved, and in certain situations taking the lead, in commercialization within the United States.

One of the key factors in our ability to form significant alliances with pharmaceutical companies is the strength of our intellectual property position relating to the development and commercialization of siRNAs as therapeutics. This includes ownership of, or exclusive rights to, issued patents and pending patent applications claiming fundamental features of siRNAs and RNAi therapeutics. These patents include those called Crooke, Kreutzer-Limmer, Glover and Hannon. In addition, the United States Patent and Trademark Office recently issued notices of allowance for two patent applications in the Tuschl II patent series that broadly cover certain features for siRNAs that we believe are needed for their use as therapeutics. These allowed patent applications are exclusively licensed to Alnylam for therapeutic applications. Our patent estate also includes a broad portfolio of intellectual property relating to chemical modifications of siRNAs licensed from Isis Pharmaceuticals, Inc., or Isis, and a number of granted and pending patent applications claiming siRNAs directed to specific targets as treatments for particular diseases.

To realize additional value from our intellectual property, we also grant licenses to biotechnology companies in our InterfeRx™ program for the development and commercialization of RNAi therapeutics for specified targets in which we have no strategic interest. InterfeRx licensees include Nastech Pharmaceutical Company Inc., or Nastech, and GeneCare Research Institute Co., Ltd., or GeneCare, while Benitec Ltd., or Benitec, has options to take InterfeRx licenses. We also license key aspects of our intellectual property to companies active in the research products and services market. As of February 28, 2006, we had granted such licenses to eleven separate companies. Our InterfeRx and research product licenses aim to generate modest near-term revenues that we can re-invest in the development of our proprietary RNAi therapeutics pipeline.

We also seek funding for the development of our proprietary RNAi therapeutics pipeline from foundations and government sources. We have obtained funding for our cystic fibrosis program from Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT. We have received a grant from the Michael J. Fox Foundation for our work on Parkinson's disease. Lastly, we have obtained initial government support for our pandemic flu program from DARPA, the Defense Advanced Research Projects Agency of the United States Department of Defense.

Alnylam Product Platform

To realize the potential of RNAi therapeutics as a broad new class of drugs, we are developing capabilities that we can apply to any specific siRNA in a relatively standard fashion to endow it with drug-like properties. We use the term product platform to describe these capabilities because we believe they will enable us to develop many products across a variety of therapeutic areas. The concept for our product platform is that it will provide a systematic approach to identifying RNAi drug candidates with the following steps:

Sequence selection. Using sophisticated bioinformatics tools we scan through the entire sequence of a target mRNA to identify sequences that are unique to that mRNA and have few closely similar sequences in other mRNAs. From these unique sequences we derive a list of potential siRNAs that would match up exactly with the target mRNA and not with any other mRNAs. We narrow this list down further by applying filters for other important properties, such as the identity of sequences in mRNAs across multiple species to facilitate pre-clinical and clinical testing. This provides us with a shorter list of siRNAs, each of which we then synthesize for experimental evaluation.

Potency selection. The siRNAs synthesized in the sequence selection step are tested in cell culture systems to compare their potencies in suppressing production of the target protein.

Stabilization by chemical modification. Each of the most potent siRNAs is assessed to identify the sites within its structure where it is most vulnerable to attack by enzymes known as ribonucleases that could degrade the siRNA. A minimal set of chemical modifications is then introduced into the siRNA to protect these vulnerable sites, and the modified siRNA is tested to confirm its stability and that it has retained activity against the target mRNA.

Improvement of biodistribution by conjugation of additional chemical groups. The stabilized siRNA is further modified by the addition, or conjugation, of one or more chemical groups designed to improve uptake of the siRNA into cells and, if desired, to prolong the time it circulates in the blood.

Formulation with appropriate delivery reagents. In addition to, or instead of, introducing chemical modifications into candidate siRNAs, we may also investigate the effect of different formulation reagents on the stability and biodistribution of these candidate siRNAs. Examples of such formulation reagents include lipids that can be used to form very small particles, known as liposomes or lipoplexes, that contain the siRNAs of interest.

We expect this process to generate RNAi drug candidates that are potent against and specific for a particular target, are appropriately stable and are able to penetrate cells of target tissues. Moreover, we expect this process for finding suitable drug candidates to be simpler, faster and more productive than the corresponding process for small molecule and protein drug candidates. Therefore, we believe that with the progress we have made and expect to make in the future in developing our product platform, we will be well positioned to pursue multiple therapeutic opportunities.

We believe that we have made considerable progress in developing our product platform, as documented in a number of publications, including papers in *Nature* and *Nature Medicine*. This progress has enabled us to initiate and advance a number of discovery and development programs for Direct RNAi therapeutics. We also expect that in the reasonably near term we will be able to initiate development programs for Systemic RNAi therapeutics. We recognize, however, that considerable challenges remain with respect to delivery of siRNAs to target cells and tissues, especially for Systemic RNAi therapeutics. We therefore regard further development of our product platform as a continuing high priority.

Product Pipeline

The following is a summary of our product pipeline as of February 28, 2006:

Program	*Partner*	*Discovery*	*Development*	*Clinical*
RSV infection	None			Phase I
Pandemic flu	Novartis			IND end 2006*
Cystic fibrosis	CFFT			
Neuropathic pain	None			
Spinal cord injury	Merck			
Parkinson's disease	Medtronic			
Huntington's disease	Medtronic			
Ocular diseases	Merck			
Novartis programs	Novartis			
Other Alnylam programs	None			

* *Submission of IND expected as early as the end of 2006*

We consider a program to be a discovery program while we are still at the stage of identifying and comparing potential drug candidates but have not yet established the timing for human clinical trials. Once such timing has been established, we consider a program to have advanced to the development stage, and to be a development program.

Our two development programs and most of our discovery programs are focused on Direct RNAi therapeutics, which we believe we can advance with the current capabilities of our product platform. As we develop these capabilities further, we expect that in the relatively near future we will be in a position to advance one or more programs for Systemic RNAi therapeutics to the development stage.

Both of our current development programs are focused on viruses that infect the respiratory tract. The more advanced of these programs is focused on RSV. We initiated human clinical trials of ALN-RSV01, our candidate RNAi therapeutic for the treatment of RSV infection, in December 2005. Our second development program is focused on pandemic flu. We expect to file an IND for an RNAi therapeutic for pandemic flu as early as the end of 2006.

We have spent substantial funds over the past three years to develop our product pipeline and expect to continue to do so in the future. We spent approximately $35.3 million in 2005, $24.6 million in 2004 and $13.1 million in 2003 on research and development activities.

Development Programs

Respiratory Syncytial Virus Infection

Market Opportunity

RSV is a highly contagious virus that causes infections in both the upper and lower respiratory tract. RSV infects nearly every child by the age of two years and, in several populations, is responsible for a significant percentage of all hospitalizations. These populations include infants born prematurely, children with lung or congenital heart disease, the elderly, and other adult immune-compromised populations. RSV infection typically results in cold-like symptoms but can lead to more serious respiratory illness such as croup, pneumonia and bronchiolitis, and in extreme cases, severe illness and death. According to the Centers for Disease Control and Prevention, or CDC, RSV is responsible for up to an estimated 100,000 pediatric hospitalizations each year in the United States. As a result, there is a significant need for novel therapeutics to treat patients who become infected with RSV.

Current Treatments

The only product currently approved for the treatment of RSV infection is Ribavirin, which is marketed as Virazole® by Valeant Pharmaceuticals International. This product has limited utilization as it is approved only for

treatment of hospitalized infants and young children with severe lower respiratory tract infections due to RSV. Moreover, administration of the drug is cumbersome and requires elaborate environmental reclamation devices because of potential harmful effects on healthcare personnel exposed to the drug.

Two products have been approved for the prevention of severe lower respiratory tract disease caused by RSV in infants at high risk of such disease. One of these is a monoclonal antibody known as Synagis®. The other, earlier, product is an immune globulin called Respigam®. Neither of these products is approved for *treatment* of an existing RSV infection.

Alnylam Program

In our pre-clinical testing, ALN-RSV01 was shown to be an RSV-specific siRNA that is effective in both preventing and treating RSV infection in mice when administered intranasally, or through the nose. ALN-RSV01 also showed no significant toxicities in IND-enabling toxicology studies. We submitted an IND for intranasal ALN-RSV01 to the United States Food and Drug Administration, or FDA, in November 2005, and initiated Phase I clinical trials on this experimental drug in December 2005 in both the United States and Europe.

The ALN-RSV01 Phase I trial in the United States is designed to enroll 35 healthy adult volunteers, and to involve intranasal administration of drug or placebo in ascending single doses across five groups of volunteers. The additional Phase I trial in Europe is designed to enroll 57 healthy adult volunteers divided into six groups. Three groups will receive drug or placebo intranasally in ascending single doses, while the other three groups will receive ascending multiple doses daily for five consecutive days. In each study, ALN-RSV01 will be evaluated for safety, tolerability and pharmacokinetics. We expect to have preliminary data available from these trials in the first half of 2006. We also expect to submit an IND amendment in the second half of 2006 for administration of ALN-RSV01 by inhalation, and are evaluating the possibility of testing ALN-RSV01 in an experimental infection model in which live RSV is administered to adult human volunteers.

Pandemic Flu

Market Opportunity

An influenza pandemic is a global outbreak that occurs when a new flu virus appears in the human population, causes serious illness and spreads easily from person to person. Over the last several years, a highly virulent new strain of avian flu known as H5N1 has become endemic in the poultry population in Southeast Asia and caused significant mortality in humans that have been infected. In recent months, H5N1 avian flu has also been detected in bird populations in Europe and Africa. The World Health Organization and CDC have expressed concern about the potential for this virus to mutate into a form that could cause a global pandemic of human disease.

Current Treatments

Current pharmaceutical products for the control of influenza infection fall into two main categories: vaccines and anti-viral drugs. Experts believe that current vaccines and existing anti-viral agents may not be sufficient to protect against newly emerging strains of influenza virus.

Effective flu vaccines are difficult to manufacture, for two main reasons. First, the virus mutates constantly over time, undergoing sufficient change between one flu season and the next that a new vaccine must be manufactured each year. Second, the manufacturing process is very labor-intensive and time-consuming, requiring incubation of the virus in fertilized chick eggs into which it has been injected. For both of these reasons, experts are concerned that if a pandemic virus were to emerge, a new vaccine would be required and there would not be enough time to manufacture it.

There are four anti-viral flu drugs currently approved in the U.S. for the treatment of influenza. Two of these drugs, Symmetrel®(amantadine) and Flumadine® (rimantadine), are older drugs that belong to a class known as ion channel inhibitors, and resistance is widespread. The other two drugs, Relenza® (zanamivir) and Tamiflu® (oseltamivir), are newer drugs that are approved to prevent, as well as to treat, influenza. Both function by blocking the activity of the viral protein known as neuraminidase, whose role is to promote release of newly

replicated viruses from cells. Resistance to Tamiflu has been reported, and it cannot be known until a pandemic virus emerges how effective the current neuraminidase inhibitors will be in controlling this virus.

Alnylam Program

The focus of our pandemic flu program is to develop an RNAi therapeutic targeting gene sequences that are highly conserved across known flu viruses. We anticipate that these sequences would remain largely unchanged in any newly emerging flu virus, so that our RNAi therapeutic could be effective in preventing and treating infection by a pandemic virus. We expect that this RNAi therapeutic could be stockpiled by governments as part of their preparations for a flu pandemic. In December 2005, we were awarded initial funding for our pandemic flu program from DARPA. In connection with this program, in February 2006, we entered into a new collaboration with Novartis to develop RNAi therapeutics for pandemic flu. We expect to submit an IND for a pandemic flu RNAi therapeutic as early as the end of 2006.

Discovery Programs

In addition to our development efforts on RSV and pandemic flu, we are conducting research activities to discover Direct RNAi therapeutics to treat various diseases of the respiratory system, the central nervous system, or CNS, and the eye. The diseases for which we have discovery programs include:

- *Cystic fibrosis,* or CF. CF is an inherited respiratory disorder caused by mutations in the gene for a protein known as the cystic fibrosis transmembrane conductance regulator, or CFTR. In most CF patients, potentially functional CFTR protein is produced but does not reach the cell surface. We are attempting to redirect this CFTR protein to the cell surface using siRNAs to silence specific genes involved in protein processing within the cell. We are conducting this work in collaboration with, and with funding from, CFFT, the drug discovery and development affiliate of the Cystic Fibrosis Foundation.
- *Spinal cord injury*, or SCI. Our SCI program is focused on a cellular system known as the Nogo pathway that appears to play a key role in blocking the regeneration of nerves in the spinal cord and brain after injury. In collaboration with Merck, we are seeking to develop an RNAi therapeutic that inhibits this pathway, thereby allowing nerves to regenerate, and potentially reducing or treating paralysis, after SCI.
- *Huntington's disease*, or HD. HD is a fatal, inherited and progressive brain disease which results in uncontrolled movements, loss of intellectual faculties and emotional disturbance. HD patients produce an altered form of a protein known as huntingtin whose presence is believed to trigger the death of important cells in the brain. In collaboration with Medtronic, we are seeking to develop a novel drug-device product incorporating an RNAi therapeutic that will protect these cells by suppressing production of huntingtin.
- *Parkinson's disease*, or PD. PD is another progressive brain disease characterized by uncontrollable tremor, and in some cases may result in dementia. Like HD, PD is believed to result from the death of certain cells in the brain, which in some cases is triggered by the presence of abnormally large amounts of a protein called alpha-synuclein. Our goal is to develop an RNAi therapeutic that will protect these cells by suppressing production of alpha-synuclein.
- *Neuropathic pain.* Neuropathic pain is chronic pain that results from injury or dysfunction of the nervous system. A protein called sodium channel NaV1.8 is believed to play an important role in causing neuropathic pain. The goal of our program is to develop an RNAi therapeutic that will suppress the production of NaV1.8 and thereby alleviate neuropathic pain.

In addition to these programs, as part of our collaborations with Merck and Novartis, we have research activities to discover Direct RNAi therapeutics directed to a number of other targets.

microRNA Technology Program

In addition to our efforts on siRNAs, we are adapting our product platform to address the therapeutic possibilities offered by microRNAs, a recently discovered class of small RNAs that use the RNAi pathway to regulate genes and have been implicated in various human diseases. In animal experiments published in *Nature* in

December 2005, we and our collaborators demonstrated that we could silence microRNAs using antagomirs, a potential new class of drugs we designed for this purpose. We expect that antagomirs may become an important component of our longer-term product platform for the development of RNAi therapeutics.

Strategic Alliances and Licenses

Strategic Alliances

We intend to form strategic alliances to gain access to the financial, technical, clinical and commercial resources necessary to develop and market RNAi therapeutics. We expect these alliances to provide us with financial support in the form of equity investments, research and development funding, license fees, milestone payments and royalties or profit sharing based on sales of RNAi therapeutics. We have formed such alliances with Merck, Novartis, and Medtronic.

Novartis

We have formed two alliances with Novartis. We refer to the first of these, which was initiated in September 2005, as the broad Novartis alliance, and to the second, which was initiated in February 2006, as the Novartis flu alliance.

In connection with the broad Novartis alliance, we entered into a series of transactions with Novartis beginning in September 2005. At that time, we and Novartis executed a stock purchase agreement and an investor rights agreement. When the transactions contemplated by the Stock Purchase Agreement closed in October 2005, the investor rights agreement became effective, and we and Novartis executed a research collaboration and license agreement.

Under the terms of the stock purchase agreement, on October 12, 2005, Novartis purchased approximately 5.3 million shares of our common stock at a purchase price of $11.11 per share for an aggregate purchase price of approximately $58.5 million, which, immediately after such issuance, represented 19.9% of our then outstanding common stock.

Under the terms of the collaboration and license agreement, the parties agreed to work together on selected targets, as defined in the collaboration and license agreement, to discover and develop therapeutics based on RNAi. The collaboration and license agreement has an initial term of three years and may be extended for two additional one-year terms at the election of Novartis. In addition, Novartis may terminate the collaboration and license agreement after a period of two years under specified circumstances or in the event that we materially breach our obligations. We may terminate the agreement with respect to particular programs, products and/or countries in the event of specified material breaches of its obligations by Novartis, or in its entirety under specified circumstances for multiple such breaches. In consideration for rights granted to Novartis under the collaboration and license agreement, Novartis made an up-front payment of $10.0 million to us in October 2005, partly to reimburse prior costs incurred by us to develop *in vivo* RNAi technology. In addition, the collaboration and license agreement includes terms under which Novartis will provide us with research funding and milestone payments as well as royalties on annual net sales of products resulting from the collaboration. The collaboration and license agreement also provides Novartis with a non-exclusive option to integrate our intellectual property relating to RNAi technology into Novartis' operations under specified circumstances. In connection with the exercise of the integration option, Novartis will be required to make additional payments to us. Under the terms of the collaboration and license agreement, we retain the right to discover, develop, commercialize or manufacture compounds that function through the mechanism of RNAi, or products that contain such compounds as an active ingredient, with respect to targets not selected by Novartis for inclusion in the collaboration, provided that Novartis has a right of first offer in the event that we propose to enter into an agreement with a third party with respect to any such target.

Under the terms of the investor rights agreement, we granted Novartis demand and piggyback registration rights under the Securities Act for the shares of our common stock held by Novartis. We also granted to Novartis rights to acquire additional equity securities in the event that we propose to sell or issue any equity securities, subject to specified exceptions, as described in the investor rights agreement, such that Novartis would be able to maintain its ownership percentage in us. Novartis agreed, until the later of (1) three years from the date of the

investor rights agreement and (2) the date of termination or expiration of the selection term, as defined in the collaboration and license agreement, not to acquire any of our securities, other than an acquisition resulting in Novartis and its affiliates beneficially owning less than 20% of our total outstanding voting securities, participate in any tender or exchange offer, merger or other business combination involving us or seek to control or influence our management, board of directors or policies, subject to specified exceptions described in the investor rights agreement.

In February 2006, we entered into the Novartis flu alliance. The agreement governing the flu alliance is structured as an addendum to the collaboration and license agreement for the broad Novartis alliance. This addendum supplements and, to the extent described therein, supersedes in relevant part the collaboration and license agreement for the broad Novartis alliance. Under the terms of the addendum, we and Novartis have joint responsibility for development of RNAi therapeutics for pandemic flu. Novartis will have primary responsibility for commercialization of such RNAi therapeutics worldwide, but we will be actively involved, and may in certain circumstances take the lead, in commercialization in the United States. We are eligible to receive significant funding from Novartis for our efforts on RNAi therapeutics for pandemic flu, and to receive a significant share of any profits.

Merck

In September 2003, we entered into a five-year strategic alliance with Merck to develop advanced RNAi technology and RNAi therapeutics. For technology development, both parties committed to devote significant human resources and expertise to the collaborative development of advanced RNAi technology. Merck will have exclusive rights to use our RNAi technology and the RNAi technology developed jointly under the collaboration solely for the identification and validation of drug targets. We will have rights to use this technology for all internal research purposes and in collaborations in which the primary purpose is the development of therapeutic products using RNAi. For therapeutics development, Merck agreed to provide us with twelve proprietary drug targets over the course of the collaboration that have well-validated roles in disease and that appear attractive as potential targets for RNAi therapeutic products. We have the right, but not the obligation, to develop siRNA drug candidates against each target provided by Merck. If we advance a candidate to a defined point in pre-clinical development, the parties will then decide whether we, Merck or the two companies together will proceed with the further development and commercialization of that candidate. For each drug candidate that Merck decides to develop, whether by itself or jointly with us, Merck will pay us a fee at the time of its decision, and will also reimburse us for one-half of the costs we incurred previously on that candidate. If the parties agree to develop a drug candidate together, we will share development expenses and co-promote the products upon terms to be determined by mutual agreement. If it is determined that Merck will develop the drug candidate without our further involvement, Merck will bear all development expenses and will pay us a royalty on product sales. Likewise, if it is determined that we will develop the drug candidate without further Merck involvement, we will bear all development expenses and will pay Merck a royalty on product sales. In that event, we would retain the right to collaborate with a third party on the development and commercialization of that drug candidate.

In connection with this alliance, Merck made a $2.0 million cash payment and $5.0 million equity investment in us during 2003. Merck made additional cash payments of $1.0 million in September 2004 and $2.0 million in December 2004, as well as an equity investment of $5.0 million in December 2004, in recognition of our having developed RNAi technology for use in live animals to a pre-specified level of performance.

In early 2005, we initiated a discovery program associated with this alliance. This discovery program focuses on a specific drug target proposed by Merck. The drug target is in the Nogo pathway, which is believed to play a key role in preventing regeneration of nerves in the central nervous system after injury, such as spinal cord injuries. An RNAi therapeutic that inhibits this pathway could potentially reduce or treat paralysis caused by such injuries.

In June 2004, we entered into a second collaboration and license agreement with Merck. The agreement is a multi-year collaboration to develop and commercialize RNAi therapeutic products for ocular diseases. This collaboration is focused on AMD and other ocular diseases caused by abnormal growth or leakage of small blood vessels in the eye. Our existing program to develop a Direct RNAi therapeutic targeting VEGF for the treatment of AMD was incorporated into the new collaboration. In September 2005, we announced that we had made the

strategic decision to place this VEFG program on hold because of the increasingly competitive landscape for VEGF targeting AMD therapeutics on the market and in late-stage human trials. Under the terms of the agreement, in 2004, we received a $2.0 million license fee from Merck as well as $1.0 million representing reimbursement of prior research and development costs we had incurred. The agreement also provides for us to work with Merck on two mutually agreed ocular targets in addition to VEGF. The parties will jointly fund the development of, and share the profits from, any RNAi therapeutic products for the United States market that result from the collaboration. We will also have the option to co-promote these RNAi therapeutic products in the United States. Marketing and sales outside of the United States will be conducted by Merck, with us receiving royalties.

CFFT

In March 2005, we entered into a collaboration with CFFT to investigate the potential for RNAi therapeutic products to treat CF. Under this collaboration, CFFT provided us with an initial payment of $0.5 million and a milestone payment of $0.3 million and may make additional milestone payments totaling an aggregate of $0.7 million based on the achievement of certain scientific milestones. In addition to funding, CFFT will provide us with access to certain scientific resources to support our siRNA discovery and development efforts. If the discovery and development efforts under this collaboration result in the identification of siRNAs that are candidates for further development, the parties will negotiate a mutually agreeable support arrangement for further phases of development. In the event that we develop a marketable therapeutic for the treatment of CF without the support of CFFT, we will be required to pay CFFT certain pre-determined payments.

Medtronic

In February 2005, we entered into a collaboration with Medtronic to pursue the potential development of therapeutic products for the treatment of neurodegenerative disorders such as Parkinson's, Huntington's and Alzheimer's disease. The collaboration is focused on developing novel drug-device combinations incorporating RNAi therapeutic products. Initially, the parties will engage in a joint technology development program for a period of two years, which can be extended by mutual agreement. This initial joint technology development program is focused on delivering candidate RNAi therapeutic products to specific areas of the brain using implantable infusion systems.

After successful completion of the initial joint technology development program, the parties must jointly determine whether to initiate product development. If the parties jointly decide to initiate product development, we would be responsible for the discovery and early development of candidate RNAi therapeutic products, and Medtronic would be responsible for late-stage development and commercialization of any drug-device products that result. Medtronic also would adapt or develop medical devices to deliver the candidate RNAi therapeutic products to targeted locations in the nervous system.

After successful completion of the initial joint technology development program and a joint decision to initiate product development, Medtronic would make an initial equity investment in us and could make additional investments upon successful completion of specified milestones. The aggregate amount of our common stock that Medtronic would purchase if a joint decision were taken to initiate product development and the specified milestones were successfully completed would be $21 million. The amount of the investment to be made at the time of the joint decision to initiate product development would be between $1.0 million and $8.0 million, as determined by us, at the then-current market price. For the purpose of this investment, the then-current market price would be equal to the twenty-day trailing average of the closing price of our common stock on the Nasdaq National Market at the end of the trading day two trading days prior to the date of the decision to initiate product development. The remaining investments of between $13.0 million and $20.0 million would be made upon the achievement of the specified milestones at a purchase price equal to 120% of the then-current market price, calculated in the same manner as described above. If either party decides not to initiate product development under the collaboration agreement, Medtronic would not be required to make any equity investment in us.

After successful completion of the initial joint technology development program and a joint decision to initiate product development, we would also be eligible to receive additional cash milestone payments for each product

developed and royalties on sales of any RNAi therapeutic component of novel drug-device combinations that result from the collaboration.

Isis Pharmaceuticals, Inc.

In March 2004, we entered into a collaboration and license agreement with Isis, a leading developer of single-stranded antisense oligonucleotide drugs that target RNA. The agreement enhanced our intellectual property position with respect to RNA-based therapeutic products and our ability to develop double-stranded RNA for RNAi therapeutic products, and provided us with the opportunity to defer investment in manufacturing technology. Isis granted us licenses to its current and future patents and patent applications relating to chemistry and to RNA-targeting mechanisms for the research, development and commercialization of double-stranded RNA products. We have the right to use Isis technologies in our development programs or in collaborations, and Isis has agreed not to grant licenses under these patents to any other organization for any dsRNA products designed to work through a RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. We granted Isis non-exclusive licenses to our current and future patents and patent applications relating to RNA-targeting mechanisms and to chemistry for research use. We also granted Isis the exclusive or co-exclusive right to develop and commercialize double-stranded RNA products against a limited number of targets. In addition, we granted Isis non-exclusive rights to our patents and patent applications for research, development and commercialization of single-stranded RNA products.

Under the terms of our agreement, we agreed to pay Isis an up-front license fee of $5 million, $3 million of which was paid upon signing of the agreement and the remaining $2 million of which was paid in January 2005. We also agreed to pay milestone payments, payable upon the occurrence of specified development and regulatory events, and royalties to Isis for each product that we or a collaborator develop utilizing Isis intellectual property. In addition, we agreed to pay to Isis a percentage of specified fees from strategic collaborations we may enter into that include access to the Isis intellectual property. In conjunction with the agreement, Isis made a $10.0 million equity investment in us. Isis also agreed to pay us a license fee, milestone payments, payable upon the occurrence of specified development and regulatory events, and royalties for each product developed by Isis or a collaborator that utilizes our intellectual property. The agreement also gives us an option to use Isis' manufacturing services for RNA-based therapeutic products.

Our agreement with Isis also gives us the exclusive right to grant sub-licenses for Isis technology to third parties with whom we are not collaborating. We may include these sub-licenses in our InterfeRx licenses. If a license includes rights to Isis' intellectual property, we will share revenues from that license equally with Isis.

If, by January 1, 2008, we or a collaborator have not completed the studies required for an IND submission or similar foreign filing for at least one product candidate involving these patent rights, Isis would have the right to grant licenses to third parties for the patents and patent applications licensed to us, thereby making our rights non-exclusive.

Licenses

To generate revenues from our intellectual property rights, we have established our InterfeRx program and our research reagents and services licensing program.

InterfeRx Program

Our InterfeRx program consists of the licensing of our intellectual property to others for the development and commercialization of RNAi therapeutic products relating to specific protein targets outside our areas of strategic focus. We expect to receive license fees, annual maintenance fees, milestone payments and royalties on sales of any resulting RNAi therapeutic products. Generally, we do not expect to collaborate with our InterfeRx licensees in the development of RNAi therapeutic products, but may do so in appropriate circumstances. To date, we have granted exclusive InterfeRx licenses to two companies: GeneCare in January 2005, and Nastech in August 2005. In the case of GeneCare, the license allows GeneCare to discover, develop, and commercialize RNAi therapeutic products directed against two DNA helicase genes associated with cancer. We retained the right to negotiate co-development and co-promotion arrangements with GeneCare for such products in the United States. In the case of Nastech, the

license allows Nastech to discover, develop, and commercialize RNAi therapeutic products directed against tumor necrosis factor-alpha, or TNF-alpha, the target of several drugs approved for the treatment of rheumatoid arthritis and other conditions. In both cases, we received an up-front cash payment, and expect to receive annual and milestone payments, all in cash, and royalties on sales of any products that result from the licensing agreement.

In April 2005, we entered into an agreement with Benitec, under which we granted Benitec options to take up to five InterfeRx exclusive licenses to pursue synthetic RNAi therapeutic products against mutually agreed, specific targets, in return for license fees, milestone payments and royalties. Under the same agreement, we also granted Benitec options to non-exclusively license our intellectual property in the field of expressed RNAi, that is, RNAi mediated by siRNAs generated from DNA constructs introduced into cells. If Benitec were to exercise any of these options, we would receive license fees and be entitled to receive milestone payments and royalties on any expressed RNAi products developed by Benitec or its licensees.

Research Reagents and Services

We have granted licenses to our intellectual property for the development and commercialization of research reagents and services, and intend to enter into additional licenses on an ongoing basis. Our target licensees are vendors that provide siRNAs and related products and services for use in biological research. We offer these licenses in return for an initial license fee, annual renewal fees and royalties from sales of siRNA research reagents and services. No single research reagent or research services license is material to our business.

Patents and Proprietary Rights

We have devoted considerable effort and resources to establish what we believe to be a strong position in intellectual property relevant to RNAi therapeutic products. In this regard, we have focused on patents, patent applications and other intellectual property covering:

- fundamental aspects of the structure and uses of siRNAs, including their use as therapeutics, and RNAi-related mechanisms;
- chemical modifications to siRNAs that improve their suitability for therapeutic uses; and
- siRNAs directed to specific targets as treatments for particular diseases.

Intellectual Property Related to Fundamental Aspects and Uses of siRNA and RNAi-related Mechanisms

In this category, we include patents and patent applications that claim key aspects of RNAi-related mechanisms. Specifically, we include patents and patent applications relating to targeted cleavage of mRNA directed by RNAi-like oligonucleotides, double-stranded RNAs of particular lengths, particular structural features of these dsRNAs, such as overhanging ends, and uses of these dsRNAs. Our strategy has been to secure rights to the potentially key patents and patent applications covering the fundamental aspects of siRNAs on an exclusive basis where possible or appropriate. The following table lists patents or patent applications to which we have secured rights that we regard as being potentially fundamental for the use of siRNAs as therapeutics.

Licensor/Patent Owner	Subject Matter	Priority Date	Inventors	Status	Alnylam Rights
Isis Pharmaceuticals	Inactivation of target mRNA	6/6/1997	S. Crooke	Issued in the United States (U.S. 5,898,031 & U.S. 6,107,094), pending in the EU	Exclusive rights for therapeutic purposes related to dsRNAs*
Carnegie Institution of Washington	Double-stranded RNAs to induce RNAi	12/23/1997	A. Fire, C. Mello	Issued in the United States (U.S. 6,506,559), pending elsewhere	Non-exclusive rights for therapeutic purposes
Alnylam	Small double-stranded RNAs as therapeutic products	1/30/1999	R. Kreutzer, S. Limmer	Granted in the EU (EP 1144623 & EP 1214945), issued in Germany and South Africa, pending in the United States and elsewhere; accepted in Australia	Owned
Cancer Research Technology Limited	RNAi uses in mammalian cells	11/19/1999	M. Zernicka-Goetz, M.J. Evans, D.M. Glover	Granted in Europe (EP 1230375), Singapore, Australia, pending rest of world	Exclusive rights for therapeutic purposes
Massachusetts Institute of Technology, Whitehead Institute, Max Planck organization**	Mediation of RNAi by siRNAs containing 21-23 base pairs	3/30/2000	D.P. Bartel, P.A. Sharp, T. Tuschl, P.D. Zamore	Pending worldwide	Non-exclusive rights for therapeutic purposes**
Max Planck organization	siRNAs with 3'-overhangs as therapeutic products	12/1/2000	T. Tuschl, S. Elbashir, W. Lendeckel	Allowed in United States (U.S. 10/832,248 & U.S. 10/832,432), pending worldwide	Exclusive rights for therapeutic purposes
Cold Spring Harbor Laboratory	RNAi uses in mammalian cells	3/16/2001	D. Beach, G. Hannon	Allowed in United States (U.S. 09/866,557), pending worldwide	Non-exclusive rights for therapeutic purposes
Stanford University	RNAi uses *in vivo*	7/23/2001	M.A. Kay, A.P. McCaffrey	Pending worldwide	Co-exclusive rights for therapeutic purposes

* We hold co-exclusive therapeutic rights with Isis. However, Isis has agreed not to license such rights to any third party, except in the context of a collaboration in which Isis plays an active role.

** We hold exclusive rights to the interest owned by three of four co-owners. The fourth co-owner, the University of Massachusetts, has licensed its interest separately to third parties.

We believe we have a strong portfolio of broad and exclusive rights to fundamental siRNA patents and patent applications. In securing these rights, we have focused on obtaining the strongest rights for those intellectual property assets we believe will be most important in providing competitive advantage with respect to RNAi therapeutic products. We note in particular the first, third and sixth patents and patent applications listed in the table above, those covering inventions by Dr. Crooke, Dr. Kreutzer and Dr. Limmer, and by Dr. Tuschl and his colleagues. We believe that the so-called Crooke patent, issued worldwide, is a broad patent covering the use of modified oligonucleotides to achieve enzyme-mediated cleavage of a target mRNA and, as such, has broad issued claims that cover RNAi. We have obtained rights to the Crooke patent through a license agreement with Isis. Under the terms of our license agreement, Isis agreed not to grant licenses under this patent to any other organization for dsRNA products designed to work through a RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. We believe the so-called Kreutzer-Limmer European patent was the first patent granted that specifically covers the use of small dsRNAs as therapeutics. Through our acquisition of Alnylam Europe in 2003, we own this patent, as well as corresponding patent applications in other countries, including the United States. The patent applications filed by the Max Planck organization on the invention by Dr. Tuschl and his colleagues, or the Tuschl II patent application, cover what we believe is a key structural feature of siRNAs, namely the presence of overhangs at the 3'-end of each of the two strands. In January 2006, we announced that United States Patent and Trademark Office had issued notices of allowance for two patent applications in the Tuschl II patent series (US Serial Nos. 10/832,248 and US 10/832,432) that broadly cover certain features for siRNAs that we believe are needed for their use as therapeutics. Following a 'Notice of Allowance', the final issuance of a patent involves several administrative steps that typically are completed within three months. We have obtained an exclusive license to claims in the Tuschl II patent series uniquely covering the use of RNAi for therapeutic purposes. The patent application contains claims relating to therapeutic uses of siRNAs with or without concomitant gene therapy. Our exclusive rights are to the claims that do not require concomitant gene therapy.

The Fire and Mello patent owned by the Carnegie Institution covers the use of dsRNAs to induce RNAi. The Carnegie Institution has made this patent broadly available for licensing and we, like many companies, have taken a non-exclusive license to the patent for therapeutic purposes. We believe, however, that the Fire and Mello patent does not claim specific structural features of dsRNAs that are important for the biological activity of siRNAs in mammalian cells. These specific features are the subjects of the Crooke patent, the Kreutzer-Limmer patent, and the Tuschl II patent application for which we have secured exclusive rights.

A first Kreutzer-Limmer patent, EP 1144623, was granted by the European Patent Office, or EPO, in 2002 and in South Africa in 2003 and is pending in other countries, including the United States. In addition, a German Utility Model covering RNAi composition was branched off the European patent application, and was registered by the German Patent and Trademark Office in 2003. A German Utility Model is a form of patent that is directed only to physical matter, such as medicines, and does not cover methods. The German Utility Model is valid for ten years from the time of the filing of its parent European patent application and is thus in effect until 2010. The issuance of the European patent is currently being opposed by several other companies under a provision of the European Patent Convention that allows such opposition. It may be several years before the outcome of this opposition is decided by the EPO.

In 2004, the Enlarged Board of Appeal, or Enlarged Board, at the EPO rendered a decision in an unrelated case covering what is known as "disclaimer practice". With a disclaimer, a patent applicant gives up, or disclaims, part of the originally claimed invention in a patent application in order to overcome prior art and adds a limitation to the claims which may have no basis in the original disclosure. The Enlarged Board determined that disclaimer practice is allowed under the European Patent Convention under a defined set of circumstances. Whether the Kreutzer-Limmer patent does fall within the allowable circumstances from the Enlarged Board will now be determined as part of the opposition proceedings regarding the Kreutzer-Limmer patent. Determination by the EPO opposition division that the use of the disclaimer in this case does not fall under one of the allowed circumstances could result in the invalidation of the current granted claims of the Kreutzer-Limmer patent. Even if the EPO opposition division determines that the use of a disclaimer is permissible, the Kreutzer-Limmer patent would remain subject to the other issues raised in the opposition. A first non-final decision in these opposition proceedings is expected in 2006. Such a non-final decision may be appealed by either of the parties so it may be several years until a final decision is reached in this opposition proceeding.

The grant of a second European patent from the Kreutzer-Limmer series, EP 1214945, originating from a divisional application of EP 1144623, was published by the EPO on June 8, 2005. Four parties each filed a Notice of Opposition opposing the grant of this second Kreutzer-Limmer patent during the period prescribed by the EPO. The EPO may rule in favor of the opponents, which could result in a patent not issuing from the EP 1214945 application.

The other pending patent applications listed in the table either provide further coverage for structural features of siRNAs or relate to the use of siRNAs in mammalian cells. For some of these, we have exclusive rights, and for others, we have non-exclusive rights. While we believe these pending patent applications are important, we also believe that access to the Crooke patent, the Kreutzer-Limmer patent and the Tuschl II patent application will be of particular importance for development and commercialization of RNAi therapeutic products, which is why we have secured exclusive positions with respect to these assets. However, because RNAi is a relatively new field, few patents have been issued, and many potentially key patent applications are still pending.

Intellectual Property Related to Chemical Modifications

Over the last fifteen years or more, a large amount of effort has been devoted by academics and other biotechnology companies to two other technologies with the potential to selectively turn off gene activity. These technologies are known as antisense oligonucleotides and ribozymes. Both involve using short DNA or RNA molecules to intercept specific mRNAs so as to reduce production of proteins encoded by these mRNAs. Scientists and companies working on antisense oligonucleotides and ribozymes have developed a variety of chemical modifications that can be applied to short DNA and RNA molecules to endow them with drug-like properties. A number of patents have been issued to these scientists and companies claiming the chemical modifications they developed. Isis has obtained many such patents. Our collaboration and license agreement with Isis that provides us with rights to use over 150 issued patents relating to chemical modifications we may wish to incorporate into our RNAi therapeutic products and rights based on future chemistry patent applications filed in the next five years to which it has rights. We believe that access to this intellectual property from Isis could accelerate our development of RNAi therapeutic products by enabling us to capitalize on proprietary chemistry developed by Isis instead of designing around this chemistry. Under the terms of our license agreement, Isis agreed not to grant licenses under these patents to any other organization for dsRNA products designed to work through a RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. One company previously involved in ribozymes, Sirna Therapeutics, Inc., or Sirna, has recently been granted a patent in the United Kingdom relating to chemically modified siRNAs.

In addition to licensing these intellectual property rights from Isis, we are also working to develop our own proprietary modifications that we can apply to siRNAs to endow them with drug-like properties. We have filed a number of patent applications relating to novel chemical modifications that we may apply to siRNAs. We filed these applications relatively recently, and are still evaluating which chemical modifications we may incorporate into siRNA drugs. We may not know for a number of years whether the modifications we use will be patentable or free of patents held by others. We note, however, that a patent in the Tuschl II patent series recently allowed in the United States claims methods for preparing siRNAs that incorporate any of various chemical modifications, including the use of phosphorothioates, 2'-O-methyl, and/or 2'-fluoro modifications. These internal and backbone modifications are believed to be important for achievement of 'drug-like' properties for RNAi therapeutics. We hold exclusive worldwide rights to these claims for RNAi therapeutics.

Intellectual Property Related to siRNAs Directed to Specific Targets

We have also filed a number of patent applications claiming specific siRNAs directed to a large number of targets as treatments for specific diseases. We recognize, however, that there may be a significant number of competing applications filed by other organizations on similar siRNAs. Because our subsidiaries, Alnylam Europe and Alnylam U.S., were among the first companies to focus on RNAi therapeutics, we believe that a number of our patent applications may predate competing applications that others may have filed. Reflecting this, in August 2005, the EPO notified us of its willingness to grant a broad patent, which we call the Kreutzer-Limmer II patent, with 103 allowed claims on therapeutic compositions, methods, and uses comprising siRNAs that are complementary to all mRNA sequences in over 125 disease target genes. These genes include targets that are part of our development and pre-clinical programs, such as those involved in the VEGF pathway and those expressed by viral pathogens

including RSV and influenza virus. In addition, the claimed targets include oncogenes, cytokines, cell adhesion receptors, angiogenesis targets, apoptosis and cell cycle targets, and additional viral disease targets such as HCV and HIV. Moreover, a patent in the Tuschl II patent series recently allowed in the United States claims methods for preparing siRNAs which mediate cleavage of an mRNA in mammalian cells, and therefore cover siRNAs directed toward any and all target genes expressed in mammalian cells. We hold exclusive worldwide rights to these claims for RNAi therapeutics.

With respect to specific siRNAs, we believe that the most important patent coverage will ultimately result from demonstrating that particular compositions exert suitable biological and therapeutic effects. Accordingly, we are focused on achieving such demonstrations for siRNAs in key therapeutic programs.

Because the work we and others are performing to develop siRNAs as drugs is at a relatively early stage, and because many patent applications on specific siRNAs are still pending, we may not know for a number of years whether any siRNA drugs we develop will be patentable and free of patents held by others. Sirna, has recently been granted two patents in the United Kingdom, one relating to targeting conserved sequences within viruses and more than one gene in a biological pathway, the other relating to siRNAs targeting the gene for a VEGF receptor. Sirna was also recently granted a patent in Australia for RNAi targeting Huntington's disease.

Competition

The pharmaceutical marketplace is extremely competitive, with hundreds of companies competing to discover, develop and market new drugs. We face a broad spectrum of current and potential competitors, ranging from very large, global pharmaceutical companies with significant resources to other biotechnology companies with resources and expertise comparable to our own. We believe that for most or all of our drug development programs, there will be one or more competing programs in other companies. In many cases, the companies with competing programs will have access to greater resources and expertise than we do and may be more advanced.

The competition we face can be grouped into three broad categories:

- Other companies working to develop RNAi therapeutic products;
- Companies developing technology known as antisense, which, like RNAi, attempts to silence the activity of specific genes by targeting the mRNAs copied from them; and
- Marketed products and development programs that compete with the drugs we may try to develop.

Other Companies Working to Develop RNAi Therapeutic Products

We are aware of several other companies that are working to develop RNAi therapeutic products. Some of these companies are seeking, as we are, to develop chemically synthesized siRNAs as drugs. Others are following a gene therapy approach, with the goal of treating patients not with synthetic siRNAs but with genes designed to produce siRNA-like molecules within cells.

Companies working on chemically synthesized siRNAs include Sirna, Acuity Pharmaceuticals, Inc., Nastech, Calando Pharmaceuticals Inc., and CytRx Corporation.

Sirna has approximately ten years' prior experience working to develop RNA molecules as drugs. This experience was largely gained with a different class of RNA molecules known as ribozymes, but could potentially be relevant for siRNAs. During 2004, Sirna initiated Phase I human clinical trials related to the development of Sirna-027, a candidate RNAi therapeutic designed to treat AMD by blocking VEGF activity. In September 2005, Sirna announced an alliance with Allergan, Inc. to develop Sirna-027 and to discover and develop other novel RNAi therapeutics against select gene targets in ophthalmic diseases. In December 2005, Sirna announced that it has selected a development candidate in its program to develop RNAi therapeutics for the treatment of hepatitis C infection, and expects to file an IND for this candidate by the fourth quarter of 2006.

Acuity Pharmaceuticals, Inc. initiated a Phase II human clinical trial in 2005 for a candidate RNAi therapeutic designed to treat AMD by blocking VEGF activity.

Nastech is developing an RNAi therapeutic directed against TNF-alpha under license from Alnylam. Separately, Nastech announced in February 2006 a program to develop RNAi therapeutics for pandemic flu and its acquisition of a flu RNAi program from Galenea Corporation.

Calando Pharmaceuticals Inc., which appears to be focused on RNAi therapeutics for the treatment of cancer, announced in February 2006 that it has established a collaborative development program relating to RNAi therapeutics with the National Cancer Institute of the National Institutes of Health, with the goal of developing RNAi therapeutic products to target neuroblastoma.

CytRx Corporation reports that it is developing RNAi therapeutics for various diseases including type 2 diabetes, obesity, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), and cytomegalovirus (CMV) infection.

Companies working on gene therapy approaches to RNAi therapeutics include Nucleonics, Inc. and Benitec Ltd.

Other Companies Working to Develop Antisense Technology

Antisense technology uses short, single-stranded, DNA-like molecules known as oligonucleotides to block mRNAs encoding specific proteins. An antisense oligonucleotide, or ASO, contains a sequence of bases complementary to a sequence within its target mRNA, enabling it to attach to the mRNA by base-pairing. The attachment of the ASO may lead to breakdown of the mRNA, or may physically block the mRNA from associating with the protein synthesis machinery of the cell. In either case, production of the protein encoded by the mRNA may be reduced. Typically, the backbone of an ASO, the linkages that hold its constituent bases together, will carry a number of chemical modifications that do not exist in naturally occurring DNA. These modifications are intended to improve the stability and pharmaceutical properties of the ASO.

While we believe that RNAi drugs may potentially have significant advantages over ASOs, including greater potency and specificity, others are developing ASO drugs that are currently at a more advanced stage of development than RNAi drugs. For example, Isis has developed an ASO drug, Vitravene, which is currently on the market, and has several ASO drug candidates in clinical trials. In addition, a number of other companies have product candidates in various stages of pre-clinical and clinical development. Included in these companies is Genta Incorporated, which has a drug candidate known as Genasense, a potential treatment for various forms of cancer. AVI BioPharma, Inc. is developing ASOs based on a type of chemistry called Morpholinos and is currently working on a program for flu. Because of their later stage of development, ASOs, rather than siRNAs, may become the preferred technology for drugs that target mRNAs in order to turn off the activity of specific genes.

Competing Drugs for RSV

The only product currently approved for the treatment of RSV infection is Ribavirin, which is marketed as Virazole® by Valeant Pharmaceuticals International. This is approved only for treatment of hospitalized infants and young children with severe lower respiratory tract infections due to RSV. However, Ribavirin has been reported to have limited efficacy and limited anti-viral activity against RSV. Moreover, administration of the drug is cumbersome and requires elaborate environmental reclamation devices because of potential harmful effects on health care personnel exposed to the drug. According to published reports by Valeant Pharmaceuticals, sales of Virazole were $15.3 million in 2005. Current RSV therapies consist of primarily treating the symptoms or preventing the viral infection by using the prophylactic drug Synagis®, which is marketed by MedImmune, Inc. Synagis is a neutralizing monoclonal antibody that prevents the virus from infecting the cell by blocking the RSV F protein that is used to infect lung cells. Synagis is injected intramuscularly once a month during the RSV season to prevent infection. According to published reports by MedImmune, Synagis sales were $1.1 billion in 2005.

Competing Drugs for Pandemic Flu

Four drugs are currently approved in the U.S. for the treatment of influenza. Two of these drugs, Symmetrel® (amantadine) and Flumadine® (rimantadine); are older drugs that belong to a class known as ion channel inhibitors. The other two drugs, Relenza® (zanamivir) and Tamiflu® (oseltamivir), were approved relatively recently, and

function by blocking the activity of the viral neuraminidase protein. Flumadine, Relenza and Tamiflu are approved to prevent as well as to treat influenza.

Symmetrel and Flumadine are effective only against influenza A viruses, and resistance is widespread. Tamiflu and Relenza are effective against both influenza A and the other main type that causes seasonal epidemics, influenza B. Resistance to Tamiflu has been reported.

The manufacturer of Tamiflu, F. Hoffman-LaRoche Ltd, or Roche, reported that 2005 sales of Tamiflu totaled 1.6 billion Swiss francs, or approximately $1.2 billion. Roche reported that these sales were driven by a severe influenza season in Japan early in the year and increased orders for pandemic readiness supplies, with over 60 countries having placed orders for pandemic stocks of Tamiflu, in some cases purchasing enough to cover 25% to 40% of their populations.

The Chief Executive Officer of GlaxoSmithKline Plc, the manufacturer of Relenza, said in February 2006 that it expects production of Relenza in 2007 to exceed the 15 million dose output in 2006, which had already been sold out.

Competing Drugs for Discovery Programs

For many of the diseases that are the subject of our RNAi therapeutics discovery programs, there are already drugs on the market or in development. These include:

- *For CF:* Current pharmaceutical treatments for CF fall into two categories. The first category consists of antibiotics formulated to treat the lung infections to which CF patients are prone. This category includes TOBI®, a tobramycin solution for inhalation marketed by Chiron Corporation, and azithromycin. The second category contains one drug, Pulmozyme®, that reduces the viscosity of the mucus that builds up in the lungs of CF patients.
- *For spinal cord injury:* There are currently no drugs approved in the United States to repair the neuronal damage associated with spinal cord injury. Patients are typically treated with methylprednisolone, an anti-inflammatory steroid that reduces the damage to neurons caused by activation of immune cells around the injury.
- *For Huntington's disease:* While certain drugs are currently used to treat some of the symptoms of Huntington's, no drug has been approved in the United States for the treatment of the underlying disease.
- *For Parkinson's disease:* Parkinson's disease is caused by the death in a specialized region of the brain of neurons that produce an important substance called dopamine. Most current drugs for Parkinson's disease work by boosting brain levels of dopamine or by mimicking its action. The primary drug for treating Parkinson's disease is typically carbidopa/levodopa, also sold as Sinemet® and Atamet®. Additional drugs include entacapone, seligiline, Mirapaz®, Perman® and Requip®. Modulation of the dopamine system only affects the symptoms of Parkinson's disease; there are no drugs approved for the treatment of the underlying disease.
- *For neuropathic pain:* A wide variety of drugs have been used to treat neuropathic pain. These include topical analgesics such as Lidoderm®, antidepressants such as amitryptyline, Paxil® and Effexor®, anti-convulsants such as carbamazepine, Neurontin® and most recently, Lyrica®, the muscle relaxant baclofen, anti-inflammatory drugs such as ibuprofen, and opioids such as oxycodone. More recently, the non-opioid drug ziconotide (Prialt®), which belongs to a new class of drugs known as N-type calcium channel blockers, was approved for treating severe chronic pain. Prialt must be administered directly into the spinal fluid using a special infusion device.

Regulatory Matters

The research, testing, manufacture and marketing of drug products and their delivery systems are extensively regulated in the United States and the rest of the world. In the United States, drugs are subject to rigorous regulation by the FDA. The Federal Food, Drug, and Cosmetic Act and other federal and state statutes and regulations govern, among other things, the research, development, testing, manufacture, storage, record keeping, packaging, labeling,

promotion and advertising, marketing and distribution of pharmaceutical products. The failure to comply with the applicable regulatory requirements may subject a company to a variety of administrative or judicially-imposed sanctions and the inability to obtain or maintain required approvals or to market approved drug products.

The steps ordinarily required before a new pharmaceutical product may be marketed in the United States include pre-clinical laboratory tests, animal tests and formulation studies, the submission to the FDA of an investigational new drug application, which must become effective prior to commencement of clinical testing, and adequate and well-controlled clinical trials to establish that the drug product is safe and effective for the indication for which FDA approval is sought. Satisfaction of FDA pre-market approval requirements typically take several years and the actual time taken may vary substantially depending upon the complexity of the product or the disease. Government regulation may delay or prevent marketing of potential products for a considerable period of time and impose costly procedures on a company's activities. Success in early stage clinical trials does not necessarily assure success in later stage clinical trials. Data obtained from clinical activities is not always conclusive and may be subject to alternative interpretations that could delay, limit or even prevent regulatory approval. Even if a product receives regulatory approval, later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market.

Pre-clinical tests include laboratory evaluation of product chemistry and formulation, as well as animal trials to assess the potential safety and efficacy of the product. The conduct of the pre-clinical tests and formulation of compounds for testing must comply with federal regulations and requirements. The results of pre-clinical testing are submitted to the FDA as part of an investigational new drug application.

A 30-day waiting period after the filing of an investigational new drug application is required prior to such application becoming effective and the commencement of clinical testing in humans. If the FDA has not commented on, or questioned, the application during this 30-day waiting period, clinical trials may begin. If the FDA has comments or questions these must be resolved to the satisfaction of the FDA prior to commencement of clinical trials. The investigational new drug application process can result in substantial delay and expense. The FDA may, at any time, impose a clinical hold on ongoing clinical trials. If the FDA imposes a clinical hold, clinical trials cannot commence or recommence without FDA authorization and then only under terms authorized by the FDA.

Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted in compliance with federal regulations and requirements, under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety and the safety and effectiveness criteria to be evaluated. Each protocol involving testing on subjects in the United States must be submitted to the FDA as part of the investigational new drug application. The study protocol and informed consent information for patients in clinical trials must be submitted to institutional review boards for approval.

Clinical trials to support new drug applications for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase I, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics and pharmacological actions and safety, including side effects associated with increasing doses. Phase II usually involves trials in a limited patient population, to determine dosage tolerance and optimum dosage, identify possible adverse effects and safety risks, and provide preliminary support for the efficacy of the drug in the indication being studied.

If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase II evaluations, Phase III trials are undertaken to further evaluate clinical efficacy and to further test for safety within an expanded patient population, typically at geographically dispersed clinical trial sites. Phase I, Phase II or Phase III testing of any product candidates may not be completed successfully within any specified time period, if at all. After successful completion of the required clinical testing, generally a new drug application is prepared and submitted to the FDA.

We believe that any Direct RNAi product candidate we develop for RSV, pandemic flu, neuropathic pain, PD, SCI, or CF will be regulated as a new drug by the FDA. FDA approval of the new drug application is required before marketing of the product may begin in the United States. The new drug application must include the results of extensive clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry,

manufacture and controls. The cost of preparing and submitting a new drug application is substantial. Under federal law, new drug applications are subject to substantial application user fees and the sponsor of an approved new drug application is also subject to annual product and establishment user fees.

The FDA has 60 days from its receipt of a new drug application to determine whether the application will be accepted for filing based on the agency's threshold determination that the new drug application is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review of the new drug application. The review process is often significantly extended by FDA requests for additional information or clarification regarding information already provided in the submission. The FDA may also refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee. The FDA normally also will conduct a pre-approval inspection to ensure the manufacturing facility, methods and controls are adequate to preserve the drug's identity, strength, quality, purity and stability, and are in compliance with regulations governing current good manufacturing practices.

If FDA evaluations of the new drug application and the manufacturing facilities are favorable, the FDA may issue an approval letter or an approvable letter followed by an approval letter. An approvable letter generally contains a statement of specific conditions that must be met in order to secure final approval of the new drug application. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of new drug application approval, the FDA may require post approval testing and surveillance to monitor the drug's safety or efficacy and may impose other conditions, including labeling restrictions which can materially impact the potential market and profitability of the drug. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

While we believe that any RNAi therapeutic we develop will be regulated as a new drug under the Federal Food, Drug, and Cosmetics Act, the FDA could decide to regulate RNAi therapeutic products as biologics under the Public Health Service Act. Biologics must have a biologics license application, or BLA, approved prior to commercialization. Like new drug applications, BLAs are subject to user fees. To obtain BLA approval, an applicant must provide pre-clinical and clinical evidence and other information to demonstrate that the biologic product is safe, pure and potent, and that the facilities in which it is manufactured, processed, packed or held meet standards, including drug good manufacturing practices and any additional standards in the license designed to ensure its continued safety, purity and potency. Biologics establishments are subject to pre-approval inspections. The review process for BLAs is time consuming and uncertain, and BLA approval may be conditioned on post approval testing and surveillance. Once granted, BLA approvals may be suspended or revoked under certain circumstances, such as if the product fails to conform to the standards established in the license.

Once a new drug application or biologics license application is approved, a product will be subject to certain post-approval requirements, including requirements for adverse event reporting and submission of periodic reports. Additionally, the FDA also strictly regulates the promotional claims that may be made about prescription drug products and biologics. In particular, the FDA requires substantiation of any claims of superiority of one product over another, including that such claims be proven by adequate and well controlled head-to-head clinical trials. To the extent that market acceptance of our products may depend on their superiority over existing therapies, any restriction on our ability to advertise or otherwise promote claims of superiority, or requirements to conduct additional expensive clinical trials to provide proof of such claims, could negatively affect the sales of our products or our costs. We must also notify the FDA of any change in an approved product beyond variations already allowed in the approval. Certain changes to the product, its labeling or its manufacturing require prior FDA approval and may require conduct of further clinical investigations to support the change. Such approvals may be expensive and time-consuming and, if not approved, the product will not be allowed to be marketed as modified.

If the FDA's evaluation of the new drug application submission or manufacturing facilities is not favorable, the FDA may refuse to approve the new drug application or issue a not approvable letter. The not approvable letter

outlines the deficiencies in the submission and often requires additional testing or information in order for the FDA to reconsider the application. Even after submitting this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. With limited exceptions, the FDA may withhold approval of a new drug application regardless of prior advice it may have provided or commitments it may have made to the sponsor.

Some of our drug candidates may need to be administered using specialized drug delivery systems. We may rely on drug delivery systems that are already approved to deliver drugs like ours to similar physiological sites or, in some instances, we may need to modify the design or labeling of the legally available device for delivery of our product candidate. In such an event, the FDA may regulate the product as a combination product or require additional approvals or clearances for the modified device. In addition, to the extent the delivery device is owned by another company, we would need that company's cooperation to implement the necessary changes to the device and to obtain any additional approvals or clearances. Obtaining such additional approvals or clearances, and cooperation of other companies, when necessary, could significantly delay, and increase the cost of obtaining, marketing approval, which could reduce the commercial viability of a drug candidate.

Once a new drug application is approved, the product covered thereby becomes a listed drug that can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application. An abbreviated new drug application provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. There is no requirement, other than the requirement for bioequivalence testing, for an abbreviated new drug application applicant to conduct or submit results of pre-clinical or clinical tests to prove the safety or effectiveness of its drug product. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, are listed as such by the FDA, and can often be substituted by pharmacists under prescriptions written for the original listed drug. Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage, dosage form, route of administration or combination, or for a new use, the approval of which was required to be supported by new clinical trials conducted by or for the sponsor. During such three-year exclusivity period, the FDA cannot grant approval of an abbreviated new drug application to commercially distribute a generic version of the drug based on that listed drug. However, the FDA can approve generic equivalents of that listed drug based on other listed drugs, such as a generic that is the same in every way but its indication for use, and thus the value of such exclusivity may be undermined. Federal law also provides a period of five years following approval of a drug containing no previously approved active ingredients, during which abbreviated new drug applications for generic versions of those drugs cannot be submitted unless the submission accompanies a challenge to a listed patent, in which case the submission may be made four years following the original product approval. Additionally, in the event that the sponsor of the listed drug has properly informed FDA of patents covering its listed drug, applicants submitting an abbreviated new drug application referencing that drug, are required to make one of four certifications, including certifying that it believes one or more listed patents are invalid or not infringed. If an applicant certifies invalidity or non-infringement, it is required to provide notice of its filing to the new drug application sponsor and the patent holder. If the patent holder then initiates a suit for patent infringement against the abbreviated new drug application sponsor within 45 days of receipt of the notice, the FDA cannot grant effective approval of the abbreviated new drug application until either 30 months has passed or there has been a court decision holding that the patents in question are invalid or not infringed. If the abbreviated new drug application applicant certifies that it does not intend to market its generic product before some or all listed patents on the listed drug expire, then the FDA cannot grant effective approval of the abbreviated new drug application until those patents expire. The first of the abbreviated new drug applicants submitting substantially complete applications certifying that listed patents for a particular product are invalid or not infringed may qualify for an exclusivity period of 180 days running from when the generic product is first marketed, during which subsequently submitted abbreviated new drug applications cannot be granted effective approval.

From time to time legislation is drafted and introduced in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of drug products. In addition, FDA regulations and guidance are often revised or reinterpreted by the agency in ways that may significantly affect our

business and our products. It is impossible to predict whether legislative changes will be enacted, or FDA regulations, guidance or interpretations changed, or what the impact of such changes, if any, may be.

Foreign Regulation of New Drug Compounds

Approval of a product by comparable regulatory authorities may be necessary in foreign countries prior to the commencement of marketing of the product in those countries, whether or not FDA approval has been obtained. The approval procedure varies among countries and can involve requirements for additional testing. The time required may differ from that required for FDA approval. Although there are some procedures for unified filings for some European countries with the sponsorship of the country which first granted marketing approval, in general, each country has its own procedures and requirements, many of which are time consuming and expensive. Thus, there can be substantial delays in obtaining required approvals from foreign regulatory authorities after the relevant applications are filed.

In Europe, marketing authorizations may be submitted at a centralized, a decentralized or a national level. The centralized procedure is mandatory for the approval of biotechnology products and provides for the grant of a single marketing authorization that is valid in all European Union member states. As of January 1995, a mutual recognition procedure is available at the request of the applicant for all medicinal products that are not subject to the centralized procedure. We will choose the appropriate route of European regulatory filing to accomplish the most rapid regulatory approvals. However, our chosen regulatory strategy may not secure regulatory approvals on a timely basis or at all.

Hazardous Materials

Our research and development processes involve the controlled use of hazardous materials, chemicals and radioactive materials and produce waste products. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of hazardous materials and waste products. We do not expect the cost of complying with these laws and regulations to be material.

Manufacturing

We have no commercial manufacturing capabilities. We may manufacture material for use in IND-enabling toxicology studies in animals, but we do not anticipate manufacturing material for human clinical use ourselves. We have contracted with Dowpharma[SM], a division of The Dow Chemical Company, for the supply of certain amounts of material to meet our testing needs for toxicology and clinical testing. Commercial quantities of any drugs that we may seek to develop will have to be manufactured in facilities, and by processes, that comply with FDA regulations and other regulations. We plan to rely on third parties to manufacture commercial quantities of any product that we successfully develop. Under our agreement with Isis, at our request, we may negotiate a manufacturing services agreement with Isis for double-stranded RNA products designated to work through an RNAi mechanism.

Scientific Advisors

We seek advice from our scientific advisory board, which consists of a number of leading scientists and physicians, on scientific and medical matters. Our scientific advisory board meets regularly to assess:

- our research and development programs;
- the design and implementation of our clinical programs;
- our patent and publication strategies;
- new technologies relevant to our research and development programs; and
- specific scientific and technical issues relevant to our business.

The current members of our scientific advisory board are:

Name	Position/Institutional Affiliation
Dennis A. Ausiello, M.D. ...	Physician-in-chief/Massachusetts General Hospital
David P. Bartel, Ph.D.	Professor/Whitehead Institute for Medical Research
Fritz Eckstein, Ph.D.	Professor/Max Planck Institute
Edward E. Harlow, Ph.D.	Professor/Harvard Medical School
Robert S. Langer, Ph.D.	Germeshausen Professor/Massachusetts Institute of Technology
Stephen N. Oesterle, M.D. ...	Senior Vice President Medicine and Technology, Medtronic, Inc.
Paul R. Schimmel, Ph.D.	Ernest and Jean Hahn Professor/Skaggs Institute for Chemical Biology
Phillip A. Sharp, Ph.D.	Institute Professor/ MIT Center for Cancer Research
Markus Stoffel, M.D., Ph.D...	Heilbrunn Professor/Rockefeller University
Thomas H. Tuschl, Ph.D.	Associate Professor/Rockefeller University
Phillip D. Zamore, Ph.D.	Professor/University of Massachusetts Medical School

Employees

As of February 28, 2006, we had 94 full-time equivalent employees, 76 of whom were engaged in research and development. None of our employees is represented by a labor union or covered by a collective bargaining agreement, nor have we experienced work stoppages. We believe that relations with our employees are good.

Financial Information About Geographic Areas

See Note 2 to our Consolidated Financial Statements, entitled "Segment and Geographic Data", for financial information about geographic areas. The Notes to our Consolidated Financial Statements are contained herein in Item 8.

Corporate Information

Alnylam Pharmaceuticals, Inc. was incorporated in Delaware in May 2003. Alnylam Europe AG, which was incorporated in Germany in June 2000 under the name Ribopharma AG, and Alnylam U.S., Inc., which was incorporated in Delaware in June 2002, are wholly owned subsidiaries of Alnylam Pharmaceuticals, Inc. Alnylam Pharmaceuticals, Inc. acquired Alnylam Europe AG in July 2003. Our principal executive office is located at 300 Third Street, Cambridge, Massachusetts 02142, and our telephone number is (617) 551-8200.

Website Access to SEC Reports

We maintain an internet website at www.alnylam.com. The information on our website is not incorporated by reference into this Annual Report on Form 10-K and should not be considered to be a part of this Annual Report on Form 10-K. Our website address is included in this Annual Report on Form 10-K as an inactive technical reference only. Our reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, including our annual reports on Form 10-K, our quarterly reports on Form 10-Q and our current reports on Form 8-K, and amendments to those reports, are accessible through our website, free of charge, as soon as reasonably practicable after these reports are filed electronically with, or otherwise furnished to, the Securities and Exchange Commission.

Executive Officers of the Registrant

Name	Age	Position
John M. Maraganore, Ph.D.	43	President, Chief Executive Officer and Director
Barry E. Greene	42	Chief Operating Officer
Vincent J. Miles, Ph.D.	55	Senior Vice President of Business Development
Patricia L. Allen	44	Vice President of Finance and Treasurer

John M. Maraganore, Ph.D. has served as our President and Chief Executive Officer and as a member of our board of directors since December 2002. From April 2000 to December 2002, Dr. Maraganore served as Senior Vice President, Strategic Product Development for Millennium Pharmaceuticals, Inc., a biopharmaceutical company.

Barry E. Greene has served as our Chief Operating Officer since he joined us in October 2003 and served as our Treasurer from February 2004 through December 2005. From February 2001 to September 2003, Mr. Greene served as General Manager of Oncology at Millennium Pharmaceuticals, Inc., a biopharmaceutical company.

Vincent J. Miles, Ph.D. has served as our Senior Vice President of Business Development since he joined us in July 2003. From May 1997 to July 2003, Dr. Miles held various positions at Millennium Pharmaceuticals, Inc., a biopharmaceutical company, including vice president positions in business development, strategic planning and scientific affairs.

Patricia L. Allen has served as our Vice President of Finance since she joined us in May 2004 and as our Treasurer since January 2006. From March 1992 to May 2004, Ms. Allen held various positions at Alkermes, Inc., a biopharmaceutical company, most recently as the Director of Finance. Ms. Allen is a certified public accountant.

ITEM 1A. RISK FACTORS.

Our business is subject to numerous risks. We caution you that the following important factors, among others, could cause our actual results to differ materially from those expressed in forward-looking statements made by us or on our behalf in filings with the SEC, press releases, communications with investors and oral statements. Any or all of our forward-looking statements in this Annual Report on Form 10-K and in any other public statements we make may turn out to be wrong. They can be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Many factors mentioned in the discussion below will be important in determining future results. Consequently, no forward-looking statement can be guaranteed. Actual future results may vary materially from those anticipated in forward-looking statements. We undertake no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise. You are advised, however, to consult any further disclosure we make in our reports filed with the SEC.

RISK FACTORS

Risks Related to Our Business

Risks Related to Being an Early Stage Company

Because we have a short operating history, there is a limited amount of information about us upon which you can evaluate our business and prospects.

Our operations began in June 2002 and we have only a limited operating history upon which you can evaluate our business and prospects. In addition, as an early stage company, we have limited experience and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to successfully:

- execute product development activities using an unproven technology;
- build and maintain a strong intellectual property portfolio;
- gain acceptance for the development and commercialization of our products;
- develop and maintain successful strategic relationships; and
- manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization.

If we are unsuccessful in accomplishing these objectives, we may not be able to develop product candidates, raise capital, expand our business or continue our operations.

The approach we are taking to discover and develop novel drugs is unproven and may never lead to marketable products.

We have concentrated our efforts and therapeutic product research on RNAi technology, and our future success depends on the successful development of this technology and products based on RNAi technology. Neither we nor any other company has received regulatory approval to market therapeutics utilizing siRNAs, the class of molecule we are trying to develop into drugs. The scientific discoveries that form the basis for our efforts to discover and develop new drugs are relatively new. The scientific evidence to support the feasibility of developing drugs based on these discoveries is both preliminary and limited. Skepticism as to the feasibility of developing RNAi therapeutics has been expressed in scientific literature. For example, there are potential challenges to achieving safe RNAi therapeutics based on the so-called off-target effects and activation of the interferon response. There are also potential challenges to achieving effective RNAi therapeutics based on the need to achieve efficient delivery into cells and tissues in a clinically relevant manner and at doses that are cost-effective.

Very few drug candidates based on these discoveries have ever been tested in animals or humans. siRNAs do not naturally possess the inherent properties typically required of drugs, such as the ability to be stable in the body long enough to reach the tissues in which their effects are required, nor the ability to enter cells within these tissues in order to exert their effects. We currently have only limited data, and no conclusive evidence, to suggest that we can introduce these drug-like properties into siRNAs. We may spend large amounts of money trying to introduce these properties, and may never succeed in doing so. In addition, these compounds may not demonstrate in patients the chemical and pharmacological properties ascribed to them in laboratory studies, and they may interact with human biological systems in unforeseen, ineffective or harmful ways. As a result, we may never succeed in developing a marketable product. If we do not successfully develop and commercialize drugs based upon our technological approach, we will not become profitable and the value of our common stock will decline.

Further, our focus solely on RNAi technology for developing drugs as opposed to multiple, more proven technologies for drug development increases the risks associated with the ownership of our common stock. If we are not successful in developing a product candidate using RNAi technology, we may be required to change the scope and direction of our product development activities. In that case, we may not be able to identify and implement successfully an alternative product development strategy.

Risks Related to Our Financial Results and Need for Financing

We have a history of losses and may never be profitable.

We have experienced significant operating losses since our inception. As of December 31, 2005, we had an accumulated deficit of $105.9 million. To date, we have not developed any products nor generated any revenues from the sale of products. Further, we do not expect to generate any such revenues in the foreseeable future. We expect to continue to incur annual net operating losses over the next several years as we expand our efforts to discover, develop and commercialize RNAi therapeutics. We anticipate that the majority of any revenue we generate over the next several years will be from collaborations with pharmaceutical companies, but cannot be certain that we will be able to secure or maintain these collaborations or to meet the obligations or achieve any milestones that we may be required to meet or achieve to receive payments. If we are unable to secure revenue from collaborations, we may be unable to continue our efforts to discover, develop and commercialize RNAi therapeutics without raising financing from other sources.

To become and remain profitable, we must succeed in developing and commercializing novel drugs with significant market potential. This will require us to be successful in a range of challenging activities, including pre-clinical testing and clinical trial stages of development, obtaining regulatory approval for these novel drugs, and manufacturing, marketing and selling them. We may never succeed in these activities, and may never generate revenues that are significant enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. If we cannot become and remain profitable, the market price of our common stock could decline. In addition, we may be unable to raise capital, expand our business, diversify our product offerings or continue our operations.

We will require substantial additional funds to complete our research and development activities and if additional funds are not available we may need to critically limit, significantly scale back or cease our operations.

We have used substantial funds to develop our RNAi technologies and will require substantial funds to conduct further research and development, including pre-clinical testing and clinical trials of any product candidates, and to manufacture and market any products that are approved for commercial sale. Because the successful development of our products is uncertain, we are unable to estimate the actual funds we will require to develop and commercialize them.

Our future capital requirements and the period for which we expect our existing resources to support our operations may vary from what we expect. We have based our expectations on a number of factors, many of which are difficult to predict or are outside of our control, including:

- our progress in demonstrating that siRNAs can be active as drugs;
- our ability to develop relatively standard procedures for selecting and modifying siRNA drug candidates;
- progress in our research and development programs, as well as the magnitude of these programs;
- the timing, receipt, and amount of milestone and other payments, if any, from present and future collaborators, if any;
- our ability to establish and maintain additional collaborative arrangements;
- the resources, time and costs required to initiate and complete our pre-clinical and clinical trials, obtain regulatory approvals, protect our intellectual property and obtain and maintain licenses to third-party intellectual property; and
- the timing, receipt and amount of sales and royalties, if any, from our potential products.

If our estimates and predictions relating to these factors are incorrect, we may need to modify our operating plan.

We will be required to seek additional funding in the future and intend to do so through either collaborative arrangements, public or private equity offerings or debt financings, or a combination of one or more of these funding sources. Additional funds may not be available to us on acceptable terms or at all. In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our stockholders will result. In addition, our investor rights agreement with Novartis provides Novartis with the right generally to maintain its ownership percentage in Alnylam. While the exercise of this right may provide us with additional funding under some circumstances, Novartis' exercise of this right will also cause further dilution to our stockholders. Debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities. If we are unable to obtain funding on a timely basis, we may be required to significantly curtail one or more of our research or development programs. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, product candidates or products that we would otherwise pursue on our own.

Risks Related to Our Dependence on Third Parties

Our collaboration with Novartis is important to our business. If this collaboration is unsuccessful, Novartis terminates this collaboration or this collaboration results in competition between us and Novartis for the development of drugs targeting the same diseases, our business could be adversely affected.

In October 2005, we entered into a collaboration agreement with Novartis. Under this agreement, Novartis will select disease targets towards which the parties will collaborate to develop drug candidates. Novartis will pay a portion of the costs to develop these drug candidates and will commercialize and market any products derived from this collaboration. In addition, Novartis will pay us certain pre-determined amounts based on the achievement of pre-clinical and clinical milestones as well as royalties on the annual net sales of any products derived from this

collaboration. This collaboration has an initial term of three years that may be extended by Novartis for two additional one-year terms. Novartis may elect to terminate this collaboration after two years under some circumstances and either party may terminate this collaboration in the event of a material uncured breach by the other party. We expect that a substantial amount of the funding for our operations will come from this collaboration. If this collaboration is unsuccessful, or if it is terminated, our business could be adversely affected.

This agreement also provides Novartis with a non-exclusive option to integrate our intellectual property into Novartis' operations and develop products without our involvement for a pre-determined fee. If Novartis elects to exercise this option, Novartis could become a competitor of ours in the development of RNAi-based drugs targeting the same diseases. Novartis has significantly greater financial resources than we do and has far more experience in developing and marketing drugs, which could put us at a competitive disadvantage if we were to compete with Novartis in the development of RNAi-based drugs targeting the same disease. The exercise by Novartis of this option could adversely affect our business.

Our agreement with Novartis allows us to continue to develop products on our own with respect to targets not selected by Novartis for inclusion in the collaboration. We may need to form additional alliances to develop products. However, our agreement with Novartis provides Novartis with a right of first offer in the event that we propose to enter into an agreement with a third party with respect to such targets. This right of first offer may make it difficult for us to form future alliances with other parties, which could impair development of our own products. If we are unable to develop products independent of Novartis, our business could be adversely affected.

We may not be able to execute our business strategy if we are unable to enter into alliances with other companies that can provide capabilities and funds for the development and commercialization of our drug candidates. If we are unsuccessful in forming or maintaining these alliances on favorable terms, our business may not succeed.

We do not have any capability for sales, marketing or distribution and have limited capabilities for drug development. Accordingly, we have entered into alliances with other companies that can provide such capabilities and may need to enter into additional alliances in the future. For example, we may enter into alliances with major pharmaceutical companies to jointly develop specific drug candidates and to jointly commercialize them if they are approved. In such alliances, we would expect our pharmaceutical collaborators to provide substantial capabilities in clinical development, regulatory affairs, marketing and sales. We may not be successful in entering into any such alliances on favorable terms due to various factors including Novartis' right of first offer. Even if we do succeed in securing such alliances, we may not be able to maintain them if, for example, development or approval of a drug candidate is delayed or sales of an approved drug are disappointing. Furthermore, any delay in entering into collaboration agreements could delay the development and commercialization of our drug candidates and reduce their competitiveness even if they reach the market. Any such delay related to our collaborations could adversely affect our business.

We entered into a collaboration agreement with Merck in September 2003, under which Merck may elect to pay a portion of the costs to develop and market certain drug candidates that we may initially develop based on information and materials provided by Merck. Merck is under no obligation to pay any of the development and commercialization costs for any of these drug candidates, and it may elect not to do so. For drug candidates from our Merck collaboration that Merck does not elect to fund, and for drug candidates we may develop outside of this collaboration, we have formed additional collaborations to fund all or part of the costs of drug development and commercialization, such as our collaboration with Novartis, the second collaboration and license agreement we entered into with Merck for ocular disease as well as collaborations with Medtronic and CFFT. We may not, however, be able to enter into additional collaborations, and the terms of any collaboration agreement we do secure may not be favorable to us. If we are not successful in our efforts to enter into future collaboration arrangements with respect to a particular drug candidate, we may not have sufficient funds to develop this or any other drug candidate internally, or to bring any drug candidates to market. If we do not have sufficient funds to develop and bring our drug candidates to market, we will not be able to generate sales revenues from these drug candidates, and this will substantially harm our business.

If any collaborator terminates or fails to perform its obligations under agreements with us, the development and commercialization of our drug candidates could be delayed or terminated.

Our dependence on collaborators for capabilities and funding means that our business would be adversely affected if any collaborator terminates its collaboration agreement with us or fails to perform its obligations under that agreement. Our current or future collaborations, if any, may not be scientifically or commercially successful. Disputes may arise in the future with respect to the ownership of rights to technology or products developed with collaborators, which could have an adverse effect on our ability to develop and commercialize any affected product candidate.

Our current collaborations allow, and we expect that any future collaborations will allow, either party to terminate the collaboration for a material breach by the other party. If a collaborator terminates its collaboration with us, for breach or otherwise, it would be difficult for us to attract new collaborators and could adversely affect how we are perceived in the business and financial communities. In addition, a collaborator could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products, either on its own or jointly with others, that may be competitive with the products on which it is collaborating with us or which could affect its commitment to the collaboration with us;
- pursue higher-priority programs or change the focus of its development programs, which could affect the collaborator's commitment to us; or
- if it has marketing rights, choose to devote fewer resources to the marketing of our product candidates, if any are approved for marketing, than it does for product candidates of its own development.

If any of these occur, the development and commercialization of one or more drug candidates could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue such development and commercialization on our own.

We have very limited manufacturing experience or resources and we must incur significant costs to develop this expertise or rely on third parties to manufacture our products.

We have very limited manufacturing experience. Our internal manufacturing capabilities are limited to small-scale production of non-GMP material for use in *in vitro* and *in vivo* experiments. In order to develop products, apply for regulatory approvals and commercialize our products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. We may manufacture clinical trial materials ourselves or we may rely on others to manufacture the materials we will require for any clinical trials that we initiate. Only a limited number of manufacturers supply synthetic RNAi. We have contracted with Dowpharma contract manufacturing services, a business unit of The Dow Chemical Company, for supply of material to meet our testing needs for toxicology and clinical testing. There are risks inherent in pharmaceutical manufacturing that could affect Dowpharma's ability to meet our delivery time requirements or provide adequate amounts of material to meet our needs. Included in these risks are synthesis failures and contamination during the manufacturing process, both of which could result in unusable product and cause delays in our development process. The manufacturing process for any products that we may develop is an element of the FDA approval process and we will need to contract with manufacturers who can meet the FDA requirements on an ongoing basis. In addition, if we receive the necessary regulatory approval for any product candidate, we also expect to rely on third parties, including our collaborators, to produce materials required for commercial production. We may experience difficulty in obtaining adequate manufacturing capacity for our needs. If we are unable to obtain or maintain contract manufacturing for these product candidates, or to do so on commercially reasonable terms, we may not be able to successfully develop and commercialize our products.

To the extent that we enter into manufacturing arrangements with third parties, we will depend on these third parties to perform their obligations in a timely manner and consistent with regulatory requirements. The failure of a

third-party manufacturer to perform its obligations as expected could adversely affect our business in a number of ways, including:

- we may not be able to initiate or continue clinical trials of products that are under development;
- we may be delayed in submitting applications for regulatory approvals for our products;
- we may lose the cooperation of our collaborators;
- we may be required to cease distribution or recall some or all batches of our products; and
- ultimately, we may not be able to meet commercial demands for our products.

If a third-party manufacturer with whom we contract fails to perform its obligations, we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different third-party manufacturer, which we may not be able to do with reasonable terms, if at all. In addition, if we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget. Furthermore, a manufacturer may possess technology related to the manufacture of our product candidate that such manufacturer owns independently. This would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our products.

We have no sales, marketing or distribution experience and expect to depend significantly on third parties who may not successfully commercialize our products.

We have no sales, marketing or distribution experience. We expect to rely heavily on third parties to launch and market certain of our product candidates, if approved. We may have limited or no control over the sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties.

To develop internal sales, distribution and marketing capabilities, we will have to invest significant amounts of financial and management resources. For products where we decide to perform sales, marketing and distribution functions ourselves, we could face a number of additional risks, including:

- we may not be able to attract and build a significant marketing or sales force;
- the cost of establishing a marketing or sales force may not be justifiable in light of the revenues generated by any particular product; and
- our direct sales and marketing efforts may not be successful.

Risks Related to Managing Our Operations

If we are unable to attract and retain qualified key management and scientists, staff consultants and advisors, our ability to implement our business plan may be adversely affected.

We are highly dependent upon our senior management and scientific staff. The loss of the service of any of the members of our senior management, including Dr. John Maraganore, our President and Chief Executive Officer, may significantly delay or prevent the achievement of product development and other business objectives. Our employment agreements with our key personnel are terminable without notice. We do not carry key man life insurance on any of our key employees.

Although we have generally been successful in our recruiting efforts, we face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions. We may be unable to attract and retain suitably qualified individuals, and our failure to do so could have an adverse effect on our ability to implement our business plan.

We may have difficulty managing our growth and expanding our operations successfully as we seek to evolve from a company primarily involved in discovery and pre-clinical testing into one that develops and commercializes drugs.

Since we commenced operations in 2002, we have grown rapidly to over 94 full time equivalent employees, with offices and laboratory space in both Cambridge, Massachusetts and Kulmbach, Germany. This rapid and substantial growth, and the geographical separation of our sites, has placed a strain on our administrative and operational infrastructure, and we anticipate that our continued growth will have a similar impact. If drug candidates we develop enter and advance through clinical trials, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with other organizations to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various collaborators, suppliers and other organizations. Our ability to manage our operations and growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures in at least two different countries. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

If we are unable to manage the challenges associated with our international operations, the growth of our business could be limited.

In addition to our operations in Cambridge, Massachusetts, we operate an office and laboratory in Kulmbach, Germany. We are subject to a number of risks and challenges that specifically relate to these international operations. Our international operations may not be successful if we are unable to meet and overcome these challenges, which could limit the growth of our business and may have an adverse effect on our business and operating results. These risks include:

- fluctuations in foreign currency exchange rates that may increase the U.S. dollar cost of our international operations;
- difficulty managing operations in multiple locations, which could adversely affect the progress of our product candidate development program and business prospects;
- local regulations that may restrict or impair our ability to conduct biotechnology-based research and development;
- foreign protectionist laws and business practices that favor local competition; and
- failure of local laws to provide the same degree of protection against infringement of our intellectual property, which could adversely affect our ability to develop product candidates or reduce future product or royalty revenues, if any, from product candidates we may develop.

Risks Related to Our Industry

Risks Related to Development, Clinical Testing and Regulatory Approval of Our Drug Candidates

Any drug candidates we develop may fail in development or be delayed to a point where they do not become commercially viable.

Pre-clinical testing and clinical trials of new drug candidates are lengthy and expensive and the historical failure rate for drug candidates is high. We currently have one product candidate in Phase I clinical trials which we call ALN-RSV01, for the treatment of RSV infection. We may not be able to advance any product candidates into clinical trials. Even if we do successfully enter into clinical studies, the results from pre-clinical testing of a drug candidate may not predict the results that will be obtained in human clinical trials. We, the FDA or other applicable regulatory authorities may suspend clinical trials of a drug candidate at any time if we or they believe the subjects or patients participating in such trials are being exposed to unacceptable health risks, or for other reasons. Among other reasons, adverse side effects of a drug candidate on subjects or patients in a clinical trial could result in the

FDA or foreign regulatory authorities suspending or terminating the trial and refusing to approve a particular drug candidate for any or all indications of use.

Clinical trials of a new drug candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the drug candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease and the eligibility criteria for the clinical trial. Delays in patient enrollment can result in increased costs and longer development times.

Clinical trials also require the review and oversight of institutional review boards, referred to as IRBs, which approve and continually review clinical investigations and protect the rights and welfare of human subjects. Inability to obtain or delay in obtaining IRB approval can prevent or delay the initiation and completion of clinical trials, and the FDA may decide not to consider any data or information derived from a clinical investigation not subject to initial and continuing IRB review and approval in support of a marketing application.

Our drug candidates that we develop may encounter problems during clinical trials that will cause us or regulatory authorities to delay or suspend these trials, or that will delay the analysis of data from these trials. If we experience any such problems, we may not have the financial resources to continue development of the drug candidate that is affected, or development of any of our other drug candidates. We may also lose, or be unable to enter into, collaborative arrangements for the affected drug candidate and for other drug candidates we are developing.

Delays in clinical trials could reduce the commercial viability of our drug candidates. Any of the following could delay our clinical trials:

- discussions with the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;
- problems in engaging IRBs to oversee trials or problems in obtaining IRB approval of studies;
- delays in enrolling patients and volunteers into clinical trials;
- high drop-out rates for patients and volunteers in clinical trials;
- negative results of clinical trials;
- inadequate supply or quality of drug candidate materials or other materials necessary for the conduct of our clinical trials;
- serious and unexpected drug-related side effects experienced by participants in our clinical trials; or
- unfavorable FDA inspection and review of a clinical trial site or records of any clinical or pre-clinical investigation.

The FDA approval process may be delayed for any drugs we develop that require the use of specialized drug delivery devices.

Some drug candidates that we develop may need to be administered using specialized drug delivery devices. We believe that any product candidate we develop for PD or other central nervous system diseases will need to be administered using such a device. For neurodegenerative diseases, we have entered into a collaboration agreement with Medtronic to pursue potential development of drug-device combinations incorporating RNAi therapeutics. We may not achieve successful development results under this collaboration and may need to seek other collaboration partners to develop alternative drug delivery systems, or utilize existing drug delivery systems, for the delivery of Direct RNAi therapeutics for these diseases. While we expect to rely on drug delivery systems that have been approved by the FDA or other regulatory agencies to deliver drugs like ours to similar physiological sites, we, or our collaborator, may need to modify the design or labeling of such delivery device for some products we may develop. In such an event, the FDA may regulate the product as a combination product or require additional approvals or clearances for the modified delivery device. Further, to the extent the specialized delivery device is owned by

another company, we would need that company's cooperation to implement the necessary changes to the device, or its labeling, and to obtain any additional approvals or clearances. In cases where we do not have an ongoing collaboration with the company that makes the device, obtaining such additional approvals or clearances and the cooperation of such other company could significantly delay and increase the cost of obtaining marketing approval, which could reduce the commercial viability of our drug candidate. In summary, we may be unable to find, or experience delays in finding, suitable drug delivery systems to administer Direct RNAi therapeutics, which could negatively affect our ability to successfully commercialize certain Direct RNAi therapeutics.

We may be unable to obtain U.S. or foreign regulatory approval and, as a result, be unable to commercialize our drug candidates.

Our drug candidates are subject to extensive governmental regulations relating to development, clinical trials, manufacturing and commercialization. Rigorous pre-clinical testing and clinical trials and an extensive regulatory approval process are required to be successfully completed in the United States and in many foreign jurisdictions before a new drug can be sold. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the drug candidates we may develop will obtain the appropriate regulatory approvals necessary for us or our collaborators to begin selling them.

We have very little experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including approval by the FDA. The time required to obtain FDA and other approvals is unpredictable but typically exceeds five years following the commencement of clinical trials, depending upon the complexity of the drug candidate. Any analysis we perform of data from pre-clinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We may also encounter unexpected delays or increased costs due to new government regulations, for example, from future legislation or administrative action, or from changes in FDA policy during the period of product development, clinical trials and FDA regulatory review.

Because the drugs we are intending to develop may represent a new class of drug, the FDA has not yet established any definitive policies, practices or guidelines in relation to these drugs. While we expect any RSV, PD, SCI, CF or pandemic flu product candidates we develop will be regulated as a new drug under the Federal Food, Drug, and Cosmetic Act, the FDA could decide to regulate them or other products we may develop as biologics under the Public Health Service Act. The lack of policies, practices or guidelines may hinder or slow review by the FDA of any regulatory filings that we may submit. Moreover, the FDA may respond to these submissions by defining requirements we may not have anticipated. Such responses could lead to significant delays in the clinical development of our product candidates. In addition, because there are approved treatments for RSV and PD, in order to receive regulatory approval, we will need to demonstrate through clinical trials that the product candidates we develop to treat these diseases, if any, are not only safe and effective, but safer or more effective than existing products.

Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenues from the particular drug candidate. Furthermore, any regulatory approval to market a product may be subject to limitations on the indicated uses for which we may market the product. These limitations may limit the size of the market for the product.

We are also subject to numerous foreign regulatory requirements governing the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. The foreign regulatory approval process includes all of the risks associated with FDA approval described above as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Approval by the FDA does not assure approval by regulatory authorities outside the United States.

If our pre-clinical testing does not produce successful results or our clinical trials do not demonstrate safety and efficacy in humans, we will not be able to commercialize our drug candidates.

Before obtaining regulatory approval for the sale of our drug candidates, we must conduct, at our own expense, extensive pre-clinical tests and clinical trials to demonstrate the safety and efficacy in humans of our drug candidates. Pre-clinical and clinical testing is expensive, difficult to design and implement, can take many years to

complete and is uncertain as to outcome. Success in pre-clinical testing and early clinical trials does not ensure that later clinical trials will be successful, and interim results of a clinical trial do not necessarily predict final results.

A failure of one of more of our clinical trials can occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, pre-clinical testing and the clinical trial process that could delay or prevent our ability to receive regulatory approval or commercialize our drug candidates, including:

- regulators or IRBs may not authorize us to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- our pre-clinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional pre-clinical testing or clinical trials or we may abandon projects that we expect to be promising;
- enrollment in our clinical trials may be slower than we currently anticipate or participants may drop out of our clinical trials at a higher rate than we currently anticipate, resulting in significant delays;
- our third party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner;
- we might have to suspend or terminate our clinical trials if the participants are being exposed to unacceptable health risks;
- regulators or IRBs may require that we hold, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements;
- the cost of our clinical trials may be greater than we anticipate;
- the supply or quality of our drug candidates or other materials necessary to conduct our clinical trials may be insufficient or inadequate; and
- the effects of our drug candidates may not be the desired effects or may include undesirable side effects or the drug candidates may have other unexpected characteristics.

Even if we obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory review. If we fail to comply with continuing U.S. and foreign regulations, we could lose our approvals to market drugs and our business would be seriously harmed.

Following any initial regulatory approval of any drugs we may develop, we will also be subject to continuing regulatory review, including the review of adverse drug experiences and clinical results that are reported after our drug products are made commercially available. This would include results from any post-marketing tests or vigilance required as a condition of approval. The manufacturer and manufacturing facilities we use to make any of our drug candidates will also be subject to periodic review and inspection by the FDA. The discovery of any previously unknown problems with the product, manufacturer or facility may result in restrictions on the drug or manufacturer or facility, including withdrawal of the drug from the market. We do not have, and currently do not intend to develop, the ability to manufacture material for our clinical trials or on a commercial scale. We may manufacture clinical trial materials or we may contract a third-party to manufacture these materials for us. Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured products ourselves, including reliance on the third-party manufacturer for regulatory compliance. Our product promotion and advertising is also subject to regulatory requirements and continuing FDA review.

If we fail to comply with applicable continuing regulatory requirements, we may be subject to fines, suspension or withdrawal of regulatory approval, product recalls and seizures, operating restrictions and criminal prosecutions.

Even if we receive regulatory approval to market our product candidates, the market may not be receptive to our product candidates upon their commercial introduction, which will prevent us from becoming profitable.

The product candidates that we are developing are based upon new technologies or therapeutic approaches. Key participants in pharmaceutical marketplaces, such as physicians, third-party payors and consumers, may not accept a product intended to improve therapeutic results based on RNAi technology. As a result, it may be more difficult for us to convince the medical community and third-party payors to accept and use our products.

Other factors that we believe will materially affect market acceptance of our product candidates include:

- the timing of our receipt of any marketing approvals, the terms of any approvals and the countries in which approvals are obtained;
- the safety, efficacy and ease of administration;
- the willingness of patients to accept relatively new routes of administration;
- the success of our physician education programs;
- the availability of government and third-party payor reimbursement;
- the pricing of our products, particularly as compared to alternative treatments; and
- the availability of alternative effective treatments for the diseases that product candidates we develop are intended to treat.

Even if we develop an RNAi therapeutic product for the prevention or treatment of infection by pandemic flu virus, governments may not elect to purchase such product, which could adversely affect our business.

The focus of our flu program is to develop an RNAi therapeutic targeting gene sequences that are highly conserved across known flu viruses. We anticipate that these sequences would remain largely unchanged in any newly emerging flu virus, so that our RNAi therapeutic could be effective in preventing and treating infection by a pandemic virus. While we expect that this RNAi therapeutic could be stockpiled by governments as part of their preparations for a flu pandemic, governments may not elect to purchase such product, which could adversely affect our business.

If we or our collaborators, manufacturers or service providers fail to comply with regulatory laws and regulations, we or they could be subject to enforcement actions, which could affect our ability to market and sell our products and may harm our reputation.

If we or our collaborators, manufacturers or service providers fail to comply with applicable federal, state or foreign laws or regulations, we could be subject to enforcement actions, which could affect our ability to develop, market and sell our products under development successfully and could harm our reputation and lead to reduced acceptance of our products by the market. These enforcement actions include:

- warning letters;
- recalls or public notification or medical product safety alerts;
- restrictions on, or prohibitions against, marketing our products;
- restrictions on importation of our products;
- suspension of review or refusal to approve pending applications;
- suspension or withdrawal of product approvals;
- product seizures;
- injunctions; and
- civil and criminal penalties and fines.

Any drugs we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, thereby harming our business.

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. Although we intend to monitor these regulations, our programs are currently in the early stages of development and we will not be able to assess the impact of price regulations for a number of years. As a result, we might obtain regulatory approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product and negatively impact the revenues we are able to generate from the sale of the product in that country.

Our ability to commercialize any products successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Even if we succeed in bringing one or more products to the market, these products may not be considered cost-effective, and the amount reimbursed for any products may be insufficient to allow us to sell our products on a competitive basis. Because our programs are in the early stages of development, we are unable at this time to determine their cost effectiveness and the level or method of reimbursement. Increasingly, the third-party payors who reimburse patients, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are challenging the prices charged for medical products. If the price we are able to charge for any products we develop is inadequate in light of our development and other costs, our profitability could be adversely affected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician. Under currently applicable law, drugs that are not usually self-administered may be eligible for coverage by the Medicare program if:

- they are incident to a physician's services;
- they are "reasonable and necessary" for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standard of medical practice;
- they are not excluded as immunizations; and
- they have been approved by the FDA.

There may be significant delays in obtaining coverage for newly-approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA. Moreover, eligibility for coverage does not imply that any drug will be reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement may be based on payments allowed for lower-cost drugs that are already reimbursed, may be incorporated into existing payments for other services and may reflect budgetary constraints or imperfections in Medicare data. Net prices for drugs may be reduced by mandatory discounts or rebates required by government health care programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage and profitable reimbursement rates from both government-funded and private payors for new drugs that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory proposals to change the healthcare system in the United States and other major healthcare markets have been proposed in recent years. These proposals have included prescription drug benefit legislation recently enacted in the United States and healthcare reform legislation recently enacted by certain states.

Further federal and state legislative and regulatory developments are possible and we expect ongoing initiatives in the United States to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from drug candidates that we may successfully develop.

Another development that may affect the pricing of drugs is Congressional action regarding drug reimportation into the United States. The Medicare Prescription Drug Plan legislation, which became law in December 2003, requires the Secretary of Health and Human Services to promulgate regulations for drug reimportation from Canada into the United States under some circumstances, including when the drugs are sold at a lower price than in the United States. The Secretary retains the discretion not to implement a drug reimportation plan if he finds that the benefits do not outweigh the cost. Proponents of drug reimportation may attempt to pass legislation that would directly allow reimportation under certain circumstances. If legislation or regulations were passed allowing the reimportation of drugs, they could decrease the price we receive for any products that we may develop, negatively affecting our anticipated revenues and prospects for profitability.

Some states and localities have established drug importation programs for their citizens. So far, these programs have not led to a large proportion of prescription orders to be placed for foreign purchase. The FDA has warned that importing drugs is illegal and in December 2004 began to take action to halt the use of these programs by filing a civil complaint against an importer of foreign prescription drugs. If such programs were to become more substantial and were not to be encumbered by the federal government, they could also decrease the price we receive for any products that we may develop, negatively affecting our anticipated revenues and prospects for profitability.

There is a substantial risk of product liability claims in our business. If we are unable to obtain sufficient insurance, a product liability claim against us could adversely affect our business.

Our business exposes us to significant potential product liability risks that are inherent in the development, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. If we succeed in marketing products, such claims could result in an FDA investigation of the safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs, and potentially a recall of our products or more serious enforcement action, or limitations on the indications for which they may be used, or suspension or withdrawal of approval. We currently do not have any product liability insurance, but plan to obtain such insurance at appropriate levels prior to initiating clinical trials and at higher levels prior to marketing any of our drug candidates. Any insurance we obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could have a material adverse effect on our business.

If we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research and development involves the use of hazardous materials, chemicals and various radioactive compounds. We maintain quantities of various flammable and toxic chemicals in our facilities in Cambridge and Germany that are required for our research and development activities. We believe our procedures for storing, handling and disposing these materials in our Cambridge facility comply with the relevant guidelines of the City of Cambridge and the Commonwealth of Massachusetts and the procedures we employ in our German facility comply with the standards mandated by applicable German laws and guidelines. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards mandated by applicable regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of these materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims

that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate any of these laws or regulations.

Risks Related to Competition

The pharmaceutical market is intensely competitive. If we are unable to compete effectively with existing drugs, new treatment methods and new technologies, we may be unable to commercialize any drugs that we develop.

The pharmaceutical market is intensely competitive and rapidly changing. Many large pharmaceutical and biotechnology companies, academic institutions, governmental agencies and other public and private research organizations are pursuing the development of novel drugs for the same diseases that we are targeting or expect to target. Many of our competitors have:

- much greater financial, technical and human resources than we have at every stage of the discovery, development, manufacture and commercialization of products;
- more extensive experience in pre-clinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing and marketing pharmaceutical products;
- product candidates that are based on previously tested or accepted technologies;
- products that have been approved or are in late stages of development; and
- collaborative arrangements in our target markets with leading companies and research institutions.

We will face intense competition from drugs that have already been approved and accepted by the medical community for the treatment of the conditions for which we may develop drugs. We also expect to face competition from new drugs that enter the market. We believe a significant number of drugs are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may try to develop drugs. For instance, we are currently evaluating RNAi therapeutics for RSV, PD and CF. Virazole is currently marketed for the treatment of certain RSV patients, numerous drugs are currently marketed for the treatment of PD and two drugs, TOBI and Pulmozyme, are currently marketed for the treatment of CF. These drugs, or other of our competitors' products, may be more effective, or marketed and sold more effectively, than any products we develop.

If we successfully develop drug candidates, and obtain approval for them, we will face competition based on many different factors, including:

- the safety and effectiveness of our products;
- the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration;
- the timing and scope of regulatory approvals for these products;
- the availability and cost of manufacturing, marketing and sales capabilities;
- price;
- reimbursement coverage; and
- patent position.

Our competitors may develop or commercialize products with significant advantages over any products we develop based on any of the factors listed above or on other factors. Our competitors may therefore be more successful in commercializing their products than we are, which could adversely affect our competitive position and business. Competitive products may make any products we develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our drug candidates. Furthermore, we also face

competition from existing and new treatment methods that reduce or eliminate the need for drugs, such as the use of advanced medical devices. The development of new medical devices or other treatment methods for the diseases we are targeting could make our drug candidates noncompetitive, obsolete or uneconomical.

We face competition from other companies that are working to develop novel drugs using technology similar to ours. If these companies develop drugs more rapidly than we do or their technologies are more effective, our ability to successfully commercialize drugs will be adversely affected.

In addition to the competition we face from competing drugs in general, we also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of several other companies that are working in the field of RNAi, including Sirna Therapeutics, Inc., Acuity Pharmaceuticals, Inc., Nucleonics, Inc., SR Pharma and CytRx Corporation. In addition, we granted licenses to Isis, GeneCare, Benitec, Nastech as well as others under which these companies may independently develop RNAi therapeutics against a limited number of targets. Any of these companies may develop its RNAi technology more rapidly and more effectively than us.

We also compete with companies working to develop antisense-based drugs. Like RNAi product candidates, antisense drugs target mRNAs in order to suppress the activity of specific genes. Isis is currently marketing an antisense drug and has several antisense drug candidates in clinical trials, and another company, Genta Inc., has multiple antisense drug candidates in late-stage clinical trials. The development of antisense drugs is more advanced than that of RNAi therapeutics and antisense technology may become the preferred technology for drugs that target mRNAs to silence specific genes.

Risks Related to Patents, Licenses and Trade Secrets

If we are not able to obtain and enforce patent protection for our discoveries, our ability to develop and commercialize our product candidates will be harmed.

Our success depends, in part, on our ability to protect proprietary methods and technologies that we develop under the patent and other intellectual property laws of the United States and other countries, so that we can prevent others from unlawfully using our inventions and proprietary information. However, we may not hold proprietary rights to some patents required for us to commercialize our proposed products. Because certain U.S. patent applications are confidential until patents issue, such as applications filed prior to November 29, 2000, or applications filed after such date which will not be filed in foreign countries, third parties may have filed patent applications for technology covered by our pending patent applications without our being aware of those applications, and our patent applications may not have priority over those applications. For this and other reasons, we may be unable to secure desired patent rights, thereby losing desired exclusivity. Further, we may be required to obtain licenses under third-party patents to market our proposed products or conduct our research and development or other activities. If licenses are not available to us on acceptable terms, we will not be able to market the affected products or conduct the desired activities.

Our strategy depends on our ability to rapidly identify and seek patent protection for our discoveries. In addition, we will rely on third-party collaborators to file patent applications relating to proprietary technology that we develop jointly during certain collaborations. The process of obtaining patent protection is expensive and time-consuming. If our present or future collaborators fail to file and prosecute all necessary and desirable patent applications at a reasonable cost and in a timely manner, our business will be adversely affected. Despite our efforts and the efforts of our collaborators to protect our proprietary rights, unauthorized parties may be able to obtain and use information that we regard as proprietary. The mere issuance of a patent does not guarantee that it is valid or enforceable, so even if we obtain patents, they may not be valid or enforceable against third parties.

Our pending patent applications may not result in issued patents. The patent position of pharmaceutical or biotechnology companies, including ours, is generally uncertain and involves complex legal and factual considerations. The standards that the United States Patent and Trademark Office, or USPTO, and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. There is also no uniform, worldwide policy regarding the subject matter and scope of claims granted or allowable in pharmaceutical or

biotechnology patents. Accordingly, we do not know the degree of future protection for our proprietary rights or the breadth of claims that will be allowed in any patents issued to us or to others.

We also rely on trade secrets, know-how and technology, which are not protected by patents, to maintain our competitive position. If any trade secret, know-how or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business and financial condition could be materially adversely affected.

We license patent rights from third party owners. If such owners do not properly maintain or enforce the patents underlying such licenses, our competitive position and business prospects will be harmed.

We are a party to a number of licenses that give us rights to third party intellectual property that is necessary or useful for our business. In particular, we have obtained licenses from Isis, Idera Pharmaceuticals, Inc., Carnegie Institution of Washington, Cancer Research Technology Limited, the Massachusetts Institute of Technology, the Whitehead Institute, Garching Innovation GmbH, representing the Max Planck Gesellschaft zur Förderung der Wissenschaften e.V., referred to as the Max Planck organization, Stanford University, Cold Spring Harbor Laboratory and the University of South Alabama. We also intend to enter into additional licenses to third party intellectual property in the future.

Our success will depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for our licensed intellectual property, in particular, those patents to which we have secured exclusive rights. Our licensors may not successfully prosecute the patent applications to which we are licensed. Even if patents issue in respect of these patent applications, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue such litigation less aggressively than we would. Without protection for the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects.

Three patents from one of our key patent families, the so-called Kreutzer-Limmer patent series of patents are the subjects of opposition proceedings in the European Patent Office and the Australian Patent Office, which could result in the invalidation of these patents.

A German Utility Model covering RNAi composition was registered in 2003, and a patent covering RNAi compositions and their use was granted by the European Patent Office, or EPO, in 2002, in South Africa in 2003 and accepted for grant in Australia in 2004. Related patent applications are pending in other countries, including the United States. A German Utility Model is a form of patent that is directed only to physical matter, such as medicines, and does not cover methods. The maximum period of protection afforded by the German Utility Model ends in 2010. After the grant by the EPO of the Kreutzer-Limmer patent, published under publication number EP 1144623B9, several oppositions to the issuance of the European patent were filed with the EPO, a practice that is allowed under the European Patent Convention. Each of the oppositions raises a number of grounds for the invalidation of the patent, including the use of disclaimer practice. The EPO opposition division in charge of the opposition proceedings may agree with one or more of the grounds and could revoke the patent in whole or restrict the scope of the claims. In June 2005 the EPO granted us a new patent covering small interfering RNAs, or siRNAs, including therapeutic compositions, methods and uses of siRNAs and derivatives with a length between 15 and 49 nucleotides. The notification grant of this patent was published on June 8, 2005 under publication number EP 1214945B1. The statutory nine month opposition period expired on March 8, 2006, with four parties filing Notices of Opposition, which could result in its invalidation. It may be several years before the outcome of any opposition proceeding is decided by the EPO. However, a first non-final decision appealable by either party is expected in 2006 in the opposition proceeding involving EP 1144623.

In addition, the Enlarged Board of Appeal at the EPO rendered a decision in an unrelated case covering what is known as "disclaimer practice". With a disclaimer, a patent applicant gives up, or disclaims, part of the originally claimed invention in a patent application in order to overcome prior art and adds a limitation to the claims which may have no basis in the original disclosure. The Enlarged Board determined that disclaimer practice is allowed under the European Patent Convention under a defined set of circumstances. It now has to be determined as part of

the opposition proceedings regarding the Kreutzer-Limmer patent whether a certain limitation introduced during the prosecution of EP 1144623 represents a disclaimer and, if so, whether the use of a disclaimer during the prosecution of this case falls within one of the allowable circumstances. Determination by the EPO opposition division that the use of the disclaimer in this case does not fall under one of the allowed circumstances could result in the invalidation of the Kreutzer-Limmer patent. Even if the EPO opposition division determines that the use of a disclaimer is permissible, the Kreutzer-Limmer patent would remain subject to the other issues raised in the opposition. In addition, the Notices of Opposition to EP 1214945 list a number of other potential reasons for invalidating the allowed claims. If one or both of the Kreutzer-Limmer patents is invalidated or limited for any reason, other companies will be better able to develop products that compete with ours, which could adversely affect our competitive business position, business prospects and financial condition.

Furthermore, one party has given notice to the Australian Patent Office, IP Australia, on March 9, 2005, that it opposes the grant of AU 778474. This Australian patent derives from the same parent international patent application that gave rise to EP 1144623 and EP 1214945 and is of similar, but not the same, scope. Like EP 1214945, its claims do not rely upon a disclaimer. The opposing party recently furnished the grounds for its opposition, and has filed for an extension until June 9, 2006, to submit documents in support of the stated grounds. Like the proceedings in the EPO, these proceedings may take several years before an outcome becomes final.

The Notices of Allowance announced for the so-called Tuschl II patent application series may not result in the issuance of United States patents or any patents that issue could be found invalid by a United States Court.

On January 17, 2006 and on January 24, 2006, we announced that the USPTO has allowed claims in two patent applications that broadly cover methods for preparing siRNAs, the molecules that mediate RNAi. The USPTO issued a 'Notice of Allowance' for patent applications 10/832,248 and 10/832,432 in the 'Tuschl II' patent series. Following a 'Notice of Allowance', the final issuance of a patent involves several administrative steps that typically are completed within three months. However, there is a risk that the USPTO could decide to re-open prosecution of the allowed patent applications, which could result in patents not issuing from these applications.

Additionally, after a patent is issued, third parties can challenge the validity and/or enforceability of the patent. If patents issue from these applications, a subsequent United States court of law may find the patents either invalid or unenforceable.

Other companies or organizations may assert patent rights that prevent us from developing and commercializing our products.

RNA interference is a relatively new scientific field that has generated many different patent applications from organizations and individuals seeking to obtain important patents in the field. These applications claim many different methods, compositions and processes relating to the discovery, development and commercialization of RNAi therapeutics. Because the field is so new, very few of these patent applications have been fully processed by government patent offices around the world, and there is a great deal of uncertainty about which patents will issue, when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference and opposition proceedings in various patent offices, relating to patent rights in the RNAi field. Others may attempt to invalidate our intellectual property rights. Even if our rights are not directly challenged, disputes among third parties could lead to the weakening or invalidation of our intellectual property rights.

In addition, there are many issued and pending patents that claim aspects of oligonucleotide chemistry that we may need to apply to our siRNA drug candidates. There are also many issued patents that claim genes or portions of genes that may be relevant for siRNA drugs we wish to develop.

Thus, it is possible that one or more organizations will hold patent rights to which we will need a license. If those organizations refuse to grant us a license to such patent rights on reasonable terms, we will not be able to market products or perform research and development or other activities covered by these patents.

If we become involved in patent litigation or other proceedings related to a determination of rights, we could incur substantial costs and expenses, substantial liability for damages or be required to stop our product development and commercialization efforts.

A third party may sue us for infringing its patent rights. Likewise, we may need to resort to litigation to enforce a patent issued or licensed to us or to determine the scope and validity of third-party proprietary rights. In addition, a third party may claim that we have improperly obtained or used its confidential or proprietary information. Furthermore, in connection with a license agreement, we have agreed to indemnify the licensor for costs incurred in connection with litigation relating to intellectual property rights. The cost to us of any litigation or other proceeding relating to intellectual property rights, even if resolved in our favor, could be substantial, and the litigation would divert our management's efforts. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of any litigation could limit our ability to continue our operations.

If any parties successfully claim that our creation or use of proprietary technologies infringes upon their intellectual property rights, we might be forced to pay damages, potentially including treble damages, if we are found to have willfully infringed on such parties' patent rights. In addition to any damages we might have to pay, a court could require us to stop the infringing activity or obtain a license. Any license required under any patent may not be made available on commercially acceptable terms, if at all. In addition, such licenses are likely to be non-exclusive and, therefore, our competitors may have access to the same technology licensed to us. If we fail to obtain a required license and are unable to design around a patent, we may be unable to effectively market some of our technology and products, which could limit our ability to generate revenues or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations. Moreover, we expect that a number of our collaborations will provide that royalties payable to us for licenses to our intellectual property may be offset by amounts paid by our collaborators to third parties who have competing or superior intellectual property positions in the relevant fields, which could result in significant reductions in our revenues from products developed through collaborations.

If we fail to comply with our obligations under any licenses or related agreements, we could lose license rights that are necessary for developing and protecting our RNAi technology and any related product candidates that we develop, or we could lose certain exclusive rights to grant sublicenses.

Our current licenses impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, royalty, diligence, sublicensing, insurance and other obligations on us. If we breach any of these obligations, the licensor may have the right to terminate the license or render the license non-exclusive, which could result in us being unable to develop, manufacture and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. In addition, while we cannot currently determine the amount of the royalty obligations we will be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

For two important pending patent applications, owned in part or solely by the Max Planck organization of Germany, our amended licenses with Garching Innovation GmbH, a related entity to the Max Planck organization, require us to maintain a minimum level of employees in Germany. If we fail to comply with this condition, the owners of the patent applications that are the subject of these licenses may have the right to grant a similar license to one other company. We regard these pending patent applications as significant because they relate to important aspects of the structure of siRNA molecules and their use as therapeutics.

We have an agreement with Isis under which we were granted licenses to over 150 patents and patent applications that we believe will be useful to the development of RNAi therapeutics. If, by January 1, 2008, we or a collaborator have not completed the studies required for an investigational new drug application filing or similar foreign filing for at least one product candidate involving these patent rights, Isis would have the right to grant licenses to third parties for these patents and patent applications, thereby making our rights non-exclusive.

Confidentiality agreements with employees and others may not adequately prevent disclosure of trade secrets and other proprietary information.

In order to protect our proprietary technology and processes, we rely in part on confidentiality agreements with our collaborators, employees, consultants, outside scientific collaborators and sponsored researchers and other advisors. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover trade secrets and proprietary information, and in such cases we could not assert any trade secret rights against such party. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

Risks Related to Our Common Stock

If our stock price fluctuates, purchasers of our common stock could incur substantial losses.

The market price of our common stock may fluctuate significantly in response to factors that are beyond our control. The stock market in general has recently experienced extreme price and volume fluctuations. The market prices of securities of pharmaceutical and biotechnology companies have been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the operating performance of these companies. These broad market fluctuations could result in extreme fluctuations in the price of our common stock, which could cause purchasers of our common stock to incur substantial losses.

We may incur significant costs from class action litigation due to our expected stock volatility.

Our stock price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development efforts, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. Recently, when the market price of a stock has been volatile as our stock price may be, holders of that stock have occasionally brought securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit of this type against us, even if the lawsuit is without merit, we could incur substantial costs defending the lawsuit. The lawsuit could also divert the time and attention of our management.

If there are substantial sales of our common stock, the price of our common stock could decline.

Substantially all of the outstanding shares of our common stock are freely tradable, tradable under Rule 144 or held by holders with demand registration rights. In connection with the follow-on public offering we completed in January 2006, our executive officers and directors entered into lock-up agreements with the underwriters for such offering. As a result of these lock-up agreements, approximately 0.6 million shares are subject to a contractual restriction on resale through May 1, 2006 or later if extended in accordance with the terms of the lock-up agreement. The market price for shares of our common stock may decline if a substantial number of shares are sold, particularly at the time the restrictions on resale lapse or are waived by the underwriters.

As of December 31, 2005, the holders of approximately 10.1 million shares of our common stock have rights to require us to file registration statements under the Securities Act of 1933, as amended, or the Securities Act, or to include their shares in registration statements that we may file in the future for ourselves or other stockholders. If our existing stockholders sell a large number of shares of our common stock or the public market perceives that existing stockholders might sell shares of common stock, the market price of our common stock could decline significantly.

Insiders have substantial influence over Alnylam and could delay or prevent a change in corporate control.

Our directors and executive officers, together with their affiliates, beneficially own, in the aggregate, approximately 15% of our outstanding common stock as of December 31, 2005. As a result, these stockholders,

if acting together, may have the ability to significantly affect the outcome of matters submitted to our stockholders for approval, including the election of directors and any merger, consolidation or sale of all or substantially all of our assets. In addition, in October 2005, Novartis purchased 19.9% of our outstanding common stock as of the date of its purchase. Accordingly, these concentrations of ownership may harm the market price of our common stock by:

- delaying, deferring or preventing a change in control of our company;
- impeding a merger, consolidation, takeover or other business combination involving our company; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our company.

Anti-takeover provisions in our charter documents and under Delaware law and our shareholder rights plan could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our certificate of incorporation and our bylaws may delay or prevent an acquisition of us or a change in our management. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include:

- a classified board of directors;
- a prohibition on actions by our stockholders by written consent;
- limitations on the removal of directors; and
- advance notice requirements for election to our board of directors and for proposing matters that can be acted upon at stockholder meetings.

In addition, in July 2005, our board of directors adopted a shareholder rights plan, the provisions of which could make it more difficult for a potential acquirer of Alnylam to consummate an acquisition transaction.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions would apply even if the proposed merger or acquisition could be considered beneficial by some stockholders.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

We have not received written comments from the staff of the SEC regarding our periodic or current reports that remain unresolved.

ITEM 2. PROPERTIES

Our operations are based primarily in Cambridge, Massachusetts and Kulmbach, Germany. As of February 28, 2006, the properties we lease are listed below:

Location	Square Feet	Type	Lease Expires	Monthly Lease Payments
Cambridge, MA	44,000	Office & laboratory	September 2011	$152,000
Kulmbach, Germany	14,000	Office & laboratory	June 2008	28,000

We also entered into a lease amendment in March 2006 to lease an additional 17,823 square feet of office and laboratory space, for which we will begin paying rent on July 1, 2006. We believe that the total space available to us

under our current leases and options will meet our needs for the foreseeable future, and that additional space would be available to us on commercially reasonable terms if it were required.

ITEM 3. LEGAL PROCEEDINGS

We are currently not a party to any material legal proceedings.

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

No matters were submitted to a vote of our security holders during the fourth quarter of 2005.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

(a) Market Information

Our common stock began trading on the NASDAQ National Market on May 28, 2004 under the symbol "ALNY". Prior to that time, there was no established public trading market for our common stock. The following table sets forth the high and low sale prices per share for our common stock on the NASDAQ National Market for the period indicated:

	2004	
Year Ended December 31:	**High**	**Low**
Second Quarter (beginning May 28, 2004)	$9.50	$5.26
Third Quarter	$8.00	$3.65
Fourth Quarter	$8.60	$5.00

	2005	
Year Ended December 31:	**High**	**Low**
First Quarter	$11.00	$6.76
Second Quarter	$ 9.00	$6.90
Third Quarter	$15.22	$6.90
Fourth Quarter	$14.85	$9.06

(b) Holders of record

As of February 28, 2006, there were approximately 83 holders of record of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of individual stockholders represented by these record holders.

(c) Dividends

We have never paid or declared any cash dividends on our common stock. We currently intend to retain any earnings for future growth and, therefore, do not expect to pay cash dividends in the foreseeable future.

(d) Securities Authorized for Issuance Under Equity Compensation Plans

Information relating to our equity compensation plans will be included in our proxy statement in connection with our 2006 Annual Meeting of Stockholders, under the caption "Equity Compensation Plan Information." That portion of our proxy statement is incorporated herein by reference.

(e) Use of Proceeds

We registered shares of our common stock in connection with our initial public offering under the Securities Act. Our Registration Statement on Form S-1 (Reg. No. 333-113162) in connection with our initial public offering was declared effective by the SEC on May 27, 2004. The offering commenced as of May 27, 2004. The offering did not terminate before any securities were sold. The offering has terminated and we sold 5,000,000 shares of our common stock in the initial public offering and an additional 750,000 shares of our common stock in connection with the exercise of an over-allotment option by the underwriters. The underwriters of the offering were Banc of America Securities LLC, Citigroup Global Markets Inc., Piper Jaffray & Co. and ThinkEquity Partners LLC. All 5,750,000 shares of our common stock registered in the offering were sold at the initial public offering price per share of $6.00. The aggregate purchase price of the offering was $34,500,000. The net offering proceeds to us after deducting total expenses were $29,884,000. We incurred total expenses in connection with the offering of $4,616,000, which consisted of direct payments of:

(i) $1,929,000 in legal, accounting and printing fees;

(ii) $2,415,000 in underwriters discounts, fees and commissions; and

(iii) $272,000 in miscellaneous expenses.

No payments for such expenses were made directly or indirectly to (i) any of our directors, officers or their associates, (ii) any person(s) owning 10% or more of any class of our equity securities or (iii) any of our affiliates. There has been no material change in the planned use of proceeds from our initial public offering as described in our final prospectus filed with the SEC pursuant to Rule 424(b).

As of December 31, 2005, we had used all of the net proceeds from our initial public offering of $29.9 million. We utilized approximately $28.1 million of the net proceeds of our initial public offering to fund our operations, approximately $1.2 million to fund capital equipment purchases and approximately $0.6 million to make interest payments on our note payable.

(f) Issuer Purchases of Equity Securities

Neither we nor any affiliated purchaser or anyone acting on behalf of us or an affiliated purchaser made any purchases of shares of our common stock in the fourth quarter of 2005.

ITEM 6. SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data are derived from our financial statements. The historical results presented are not necessarily indicative of future results. The consolidated statement of operations data for the years ended December 31, 2005, 2004 and 2003 and the consolidated balance sheet data as of December 31, 2005 and 2004 have been derived from our audited consolidated financial statements included elsewhere in this Annual Report on Form 10-K. The selected consolidated financial data set forth below should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the financial statements, and the related Notes, included elsewhere in this Annual Report on Form 10-K.

In July 2003, we acquired Ribopharma AG, now called Alnylam Europe AG, a RNAi company based in Kulmbach, Germany. As a result, the quarter ended September 30, 2003 was the first quarter that included the operations of Alnylam Europe AG in our consolidated results. As such, the presentation of historical financial information and any discussion regarding the comparison of historical financial information to financial information for the year ended December 31, 2003 does not include any financial information for Alnylam Europe AG prior to July 31, 2003, unless otherwise indicated.

Selected Consolidated Financial Data
(In thousands, except per share data)

	Year Ended December 31,			Period from Inception (June 14, 2002) through December 31,
	2005	2004	2003	2002
Statement of Operations Data:				
Net revenues	$ 5,716	$ 4,278	$ 176	$ —
Operating expenses(1)	49,188	36,542	25,233	4,222
Loss from operations	(43,472)	(32,264)	(25,057)	(4,222)
Net loss	(42,914)	(32,654)	(25,033)	(4,136)
Net loss attributable to common stockholders	$(42,914)	$(35,367)	$(27,939)	$(4,884)
Net loss per common share — basic and diluted	$ (1.96)	$ (2.98)	$ (29.64)	$(14.74)
Weighted average shares outstanding — basic and diluted	21,949	11,886	943	331
(1) Non-cash stock-based compensation included in operating expenses	$ 4,597	$ 4,106	$ 3,455	$ 172

	December 31,			
	2005	2004	2003	2002
Balance Sheet Data:				
Cash, cash equivalents and short-term investments	$80,002	$46,046	$ 23,193	$15,477
Working capital	63,930	41,606	20,345	12,846
Total assets	98,348	66,107	35,183	16,111
Note payable	7,395	7,201	1,859	—
Redeemable convertible preferred stock	—	—	55,189	18,084
Total stockholders' equity (deficit)	61,779	46,142	(26,707)	(4,646)

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with the financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties. The statements contained in this Annual Report on Form 10-K that are not purely historical are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Without limiting the foregoing, the words "may," "will," "should," "could," "expects," "plans," "intends," "anticipates," "believes," "estimates," "predicts," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements. All forward-looking statements included in this Annual Report on Form 10-K are based on information available to us up to, and including the date of this document, and we assume no obligation to update any such forward-looking statements. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain important factors, including those set forth under "Management's Discussion and Analysis of Financial Condition and Results of Operations" below and Item 1A above and elsewhere in this Annual Report on Form 10-K. You should carefully review those factors and also carefully review the risks outlined in other documents that we file from time to time with the Securities and Exchange Commission.

Overview

We are a biopharmaceutical company seeking to develop and commercialize new drugs that work through a recently discovered mechanism in cells known as RNA interference, or RNAi. We believe that RNAi therapeutics have the potential to become a major class of drugs with applications in a wide range of therapeutic areas. We have initiated programs to develop RNAi therapeutics that will be administered directly to diseased parts of the body, which we call Direct RNAi™ therapeutics. We are also working to extend our capabilities by investing in RNAi therapeutics that will be administered systemically in order to treat a broad range of diseases, which we call Systemic RNAi™ therapeutics. To realize the potential of RNAi therapeutics, we are developing capabilities that we can apply to any specific small interfering RNA, or siRNA, in a systematic way to endow it with drug-like properties. We use the term "product platform" to describe these capabilities because we believe they will enable us to develop many products across a variety of therapeutic areas. We have not received regulatory approval to market any therapeutics. In November 2005, we submitted an investigational new drug application, or IND, to the U.S. Food and Drug Administration, or FDA, to initiate a human clinical trial of ALN-RSV01, our proprietary RNAi therapeutic for the treatment of patients with respiratory syncytial virus, or RSV, infection. We initiated human clinical trials of ALN-RSV01 in December 2005.

We commenced operations in June 2002. Since our inception, we have generated significant losses. As of December 31, 2005, we had an accumulated deficit of $105.9 million. Through December 31, 2005, we have funded our operations primarily through the net proceeds of $148.3 million from the sale of equity securities, including $29.9 million in net proceeds from the sale of 5.75 million shares of our common stock from our initial public offering in June 2004 and $58.4 million in net proceeds from the sale of approximately 5.3 million shares of our common stock to Novartis Pharma AG, or Novartis, in October 2005. In January 2006, we raised approximately $62.3 million of net proceeds from a follow-on public offering of approximately 5.1 million shares of our common stock. Through December 31, 2005, a substantial portion of our total net revenues have been derived from our two strategic alliances with Merck and Co., Inc., or Merck. In September 2003, we began working with Merck under a collaboration agreement for the development of RNAi-based technology and therapeutics. In June 2004, we began working with Merck under a cost sharing collaboration agreement for the co-development of Direct RNAi therapeutics for the treatment of ocular diseases. We expect our revenues to continue to be derived primarily from strategic alliances, such as our collaborations with Novartis and collaborations with Merck, and license fee revenues.

We have focused our efforts since inception primarily on business planning, research and development, acquiring intellectual property rights, recruiting management and technical staff, and raising capital. We currently have programs focused in a number of therapeutic areas, however, we are unable to predict when, if ever, we will be able to commence sales of any product. We have not achieved profitability on a quarterly or annual basis and we

expect to incur significant additional losses over the next several years. We expect our net losses to increase primarily due to research and development activities relating to our collaborations, drug development programs and other general corporate activities. We anticipate that our operating results will fluctuate for the foreseeable future. Therefore, period-to-period comparisons should not be relied upon as predictive of the results in future periods. Our sources of potential funding for the next several years are expected to include proceeds from the sale of equity, license and other fees, funded research and development payments, proceeds from equipment lines of credit and milestone payments under existing and future collaborative arrangements.

Research and Development

Since our inception, we have focused on drug discovery and development programs. Research and development expenses represent a substantial percentage of our total operating expenses. We have initiated programs to identify specific RNAi therapeutics that will be administered directly to diseased parts of the body, which we refer to as Direct RNAi drug candidates, and we expect to initiate additional programs as the capabilities of our product platform evolve. Included in our current programs are development programs, those which we have established targeted timing for human clinical trials, and discovery programs, those programs for which we have yet to establish programs for targeted timing for human clinical trials. Our most advanced development program is focused on RSV. In November 2005, we filed an IND related to our RSV program and initiated human clinical trials of ALN-RSV01 in December 2005. Our second development program is focused on another lung infection, influenza, or flu. We expect to submit an IND for an RNAi therapeutic for pandemic flu as early as the end of 2006. We also have discovery programs to develop Direct RNAi therapeutics for the treatment of the genetic respiratory disease known as cystic fibrosis, central nervous system disorders such as spinal cord injury, Parkinson's disease, Huntington's disease and neuropathic pain; ocular diseases such as age-related macular degeneration; and several other diseases that are the subject of collaborations with Merck and Novartis.

A significant component of our business strategy is to enter into strategic alliances and collaborations with pharmaceutical companies, academic institutions, research foundations and others, as appropriate, to gain access to funding, technical resources and intellectual property to further our development efforts and to generate revenues. We have entered into license agreements with Garching Innovation GmbH, or Garching, and Isis Pharmaceuticals, Inc., or Isis, as well as a number of other entities, to obtain rights to important intellectual property in the field of RNAi. We have entered into two collaborations with Novartis, to discover and develop therapeutics based on RNAi and to develop an RNAi therapeutic for pandemic flu. We have entered into collaboration agreements with Merck for the development of RNAi technology and therapeutics and the development of RNAi therapeutics for the treatment of ocular diseases. In addition, we have entered into an agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, to obtain funding and technical resources for our CF program. We also have a collaboration with Medtronic, a leading medical technology company, to focus on developing novel drug-device combinations incorporating RNAi therapeutics for the treatment of neurodegenerative diseases such as PD, Huntington's and Alzheimer's. In addition, we have collaborations with the Mayo Foundation for Medical Education and Research and the Mayo Clinic Jacksonville to explore the potential of an RNAi-based treatment for PD, and with researchers from the University of Georgia and St. Jude Children's Research Hospital to discover and develop a Direct RNAi therapeutic for the treatment and prevention of influenza, as well as other collaborations in connection with our RSV program.

There is a risk that any drug discovery and development program may not produce revenue because of the risks inherent in drug discovery and development. Moreover, there are uncertainties specific to any new field of drug discovery, including RNAi. The successful development of any product candidate we develop is highly uncertain. Due to the numerous risks associated with developing drugs, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts necessary to complete the development of, or the period in which material net cash inflows are expected to commence from, any potential product candidate. These risks include the uncertainty of:

- our ability to progress any product candidates into pre-clinical and clinical trials;
- the scope, rate and progress of our pre-clinical trials and other research and development activities;
- the scope, rate of progress and cost of any clinical trials we commence;

- clinical trial results;
- the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- the terms and timing of any collaborative, licensing and other arrangements that we may establish;
- the cost and timing of regulatory approvals;
- the cost and timing of establishing sales, marketing and distribution capabilities;
- the cost of establishing clinical and commercial supplies of any products that we may develop; and
- the effect of competing technological and market developments.

Any failure to complete any stage of the development of any potential products in a timely manner could have a material adverse effect on our operations, financial position and liquidity. A discussion of some of the risks and uncertainties associated with completing our projects on schedule, or at all, and the potential consequences of failing to do so, are set forth in Item 1A above.

Acquisition

In July 2003, we acquired a development stage enterprise called Ribopharma AG, now called Alnylam Europe AG, an RNAi therapeutics company based in Kulmbach, Germany. To effect the acquisition, we paid $1.5 million in cash and transaction costs of $0.4 million and issued common shares with a fair value of $1.9 million. In addition, we assumed $7.1 million in debt, of which $3.0 million was subsequently paid in cash and $4.1 million was settled through the issuance of shares of Series B redeemable convertible preferred stock. As a result of the acquisition, we expensed $4.6 million in 2003 of purchased in-process research and development and allocated $5.8 million to long lived assets representing the value ascribed to the Alnylam Europe work force, core technology and fixed assets acquired in the transaction. The results of Alnylam Europe are included in our consolidated results from the date of acquisition.

Critical Accounting Policies and Estimates

While our significant accounting policies are more fully described in the notes to our consolidated financial statements included in this Annual Report on Form 10-K, we believe the following accounting policies to be the most critical in understanding the judgments and estimates we use in preparing our consolidated financial statements:

Use of Estimates

Our discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of our consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses. On an ongoing basis, we evaluate our estimates and judgments, including those related to revenue recognition and accrued expenses. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions and could have a material impact on our reported results.

Accounting for Stock-Based Compensation

Employee stock awards granted under our compensation plans are accounted for in accordance with Accounting Principles Board, or APB, Opinion No. 25, Accounting for Stock Issued to Employees, or APB 25, and related interpretations. We have not adopted the fair value method of accounting for stock-based awards. All stock-based awards granted to non-employees are accounted for at their fair value in accordance with Financial Accounting Standards Board, or FASB, Statement of Financial Accounting Standards, or SFAS No. 123, or

SFAS 123, as amended, and Emerging Issues Task Force, or EITF Issue No. 96-18, Accounting for Equity Instruments that are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling, Goods or Services, or EITF 96-18, under which compensation expense is generally recognized over the vesting period of the award.

Under the intrinsic value method, compensation associated with stock-based awards to employees is determined as the difference, if any, between the current fair value of the underlying common stock on the date compensation is measured and the price an employee must pay to exercise the award. The measurement date for employee awards is generally the grant date. Under the fair-value method, compensation associated with stock-based awards to non-employees is determined based on the estimated fair value of the award itself, measured using an established option pricing model. The measurement date for non-employee awards is generally the date performance of services is complete.

During 2003, with respect to our estimates involved in the determination of the fair value of our common stock, the board of directors evaluated several events that provided indicators of the fair value of our common stock including (1) a valuation that was performed in connection with the acquisition of Alnylam Europe in July 2003, (2) the fair value of our Series B and Series C convertible preferred stock that was issued in July, September and October 2003, and its relation to the value of our common stock, and (3) the impact of our initial public offering of common stock. These factors indicated that the options granted to employees during 2003 and prior to our initial public offering in 2004 had a deemed fair value that was higher than the exercise price. This caused us to record deferred compensation of $3.7 million during 2004 and $3.3 million during 2003 and related compensation expense of $1.8 million, $3.1 million and $0.7 million in 2005, 2004 and 2003, respectively. Deferred compensation is amortized as an expense over the vesting period of the underlying stock options in accordance with the method prescribed by FASB Interpretation No. 28, Accounting for Stock Appreciation Rights and Other Variable Stock Options and Award Plans, or FIN 28, as this method appropriately matches the compensation expense related to the services performed by the option holder with the period over which each of the options vest from the date of grant.

In connection with stock options granted to non-employees for services during 2005 and 2004 and our determination of the fair value of our common stock, we have recorded cumulative deferred compensation of approximately $2.5 million, which represents the fair value of non-employee grants. The deferred compensation is recorded as an expense over the vesting period of the underlying stock options in accordance with the method prescribed by FIN 28. At the end of each financial reporting period prior to vesting, the value of these options, as calculated using the Black-Scholes option pricing model, is re-measured using the then-current fair value of our common stock. At that point, deferred compensation and the non-cash compensation recognized during that period is adjusted accordingly. Stock-based compensation expense related to these non-employee options for 2005 and 2004 was $1.2 million and $0.7 million, respectively. The deferred compensation balance at December 31, 2005 related to these awards was $1.3 million. Since the fair value of the common stock issued to non-employees is subject to change in the future, the compensation expense recognized during the year ended December 31, 2005 and prior years may not be indicative of future compensation charges.

We have also recorded cumulative deferred compensation of $3.7 million related to restricted stock awards that were issued to non-employees in 2002. Shares remaining unvested or subject to forfeiture for non-employees still providing services are subject to a mark-to-market adjustment during each reporting period prior to vesting in full. The deferred compensation is recorded as an expense over the vesting period of the underlying restricted stock in accordance with the method prescribed by FIN 28. We recorded non-cash stock-based compensation expense of $1.0 million, $0.2 million and $2.2 million during the years ended December 31, 2005, 2004 and 2003, respectively, related to the amortization of the deferred compensation. The deferred compensation balance at December 31, 2005 related to these awards was $0.1 million. Since the fair value of the common stock issued to non-employees is subject to change in the future, the compensation expense recognized during the year ended December 31, 2005 and prior years may not be indicative of future compensation charges.

Acquired and Licensed Technology

We have licensed technology that we expect to utilize in our research and development activities. The terms of the licenses may provide for up-front payments, annual maintenance payments, milestone payments based upon the

achievement of specified events and royalties based on product sales. We account for the costs associated with obtaining licenses in accordance with FASB Statement No. 2, Accounting for Research and Development Costs. Under this standard, we determine whether the technology we are licensing relates to a particular research and development project with no alternative use. If it is determined that there are no alternative uses, the amount is expensed as incurred. Alternatively, the costs are capitalized and amortized over their estimated useful life. As part of the Alnylam Europe acquisition in 2003, we have capitalized $3.6 million of core technology, with a 10-year estimated useful life and expensed $4.6 million of purchased in-process research and development that was believed to have no alternative uses.

Long-lived Assets

We generally depreciate property and equipment using the straight-line method over the asset's estimated economic life, which ranges from two years to eight years. Determining the economic lives of property and equipment requires us to make significant judgments that can materially impact our operating results. As of December 31, 2005, there was approximately $2.5 million of intangible assets on our consolidated balance sheet, including $2.3 million of core technology and $0.2 million related to the Alnylam Europe workforce. We amortize acquired intangible assets using the straight-line method over their estimated economic lives, which range from four years to 10 years. Determining the economic lives of long-lived assets requires us to make significant judgments and estimates that can materially impact our operating results. If our estimates require adjustment, it could have a material impact on our reported results.

Our policy regarding long-lived assets is to evaluate the recoverability or usefulness of these assets when the facts and circumstances suggest that these assets may be impaired. This analysis relies on a number of factors, including changes in strategic direction, business plans, regulatory developments, economic and budget projections, technological improvements and operating results. The test of recoverability or usefulness is a comparison of the asset value to the undiscounted cash flow of its expected cumulative net operating cash flow over the asset's remaining useful life. Any write-downs would be treated as permanent reductions in the carrying amount of the asset and an operating loss would be recognized. To date, we have had recurring operating losses and the recoverability of our long-lived assets is contingent upon executing our business plan that includes obtaining significant revenue from research collaborations. If we are unable to execute our business plan, we may be required to write down the value of our long-lived assets in future periods.

In accounting for the acquisition of Alnylam Europe, we allocated the purchase price to the fair value of the acquired tangible and intangible assets, including purchased in-process research and development, which requires us to make several significant judgments and estimates. In preparing the allocation, we used a discounted cash flow model to value the intangibles of Alnylam Europe, which requires us to make assumptions and estimates about, among other things: (1) the time and investment that will be required to develop the projects and related technologies; (2) the amount of revenues, royalties and milestone payments that will be derived from the projects; and (3) the appropriate discount rates to be used in the analysis. Use of different estimates and judgments could yield materially different results in our analysis, and could result in materially different asset values and purchased in-process research and development charges.

Revenue Recognition

We recognize revenue in accordance with the Securities and Exchange Commission's Staff Accounting Bulletin No. 104, Revenue Recognition in Financial Statements. Revenues from our collaboration agreements with Merck and Novartis may include nonrefundable license fees, milestones, cost reimbursements research and development funding and royalties. When evaluating multiple element arrangements, we consider whether the components of the arrangement represent separate units of accounting as defined in EITF Issue No. 00-21, Revenue Arrangements with Multiple Deliverables, or EITF 00-21. Application of these standards requires subjective determinations and requires management to make judgments about the value of the individual elements and whether it is separable from the other aspects of the contractual relationship. To date, we have determined that our up-front non-refundable license fees cannot be separated from our ongoing collaborative activities, and accordingly, do not treat them as a separate element. Nonrefundable license fees are recognized as revenue as we perform under the collaboration agreement. Where our level of effort is relatively constant over the performance period, we recognize

total fixed or determined contract revenues on a straight-line basis over the estimated period of performance under the contract.

We recognize milestone payments as revenue upon achievement of the milestone only if (1) the milestone payments are nonrefundable; (2) substantive effort is involved in achieving the milestone; and (3) the amount of the milestone is reasonable in relation to the effort expended or the risk associated with achievement of the milestone. If any of these conditions are not met, we defer the milestone payments and recognize them as revenue over the term of the contract as we complete our performance obligations. In December 2004, we recognized revenue related to the receipt of a $2.0 million technology milestone from Merck under our collaboration agreement for the development of Systemic RNAi therapeutics.

Merck

We recognize revenues from reimbursable research and development activities at the time these activities are performed under the terms of the related agreement, when the collaborator is obligated to pay and when no future performance obligations exist. In revenue arrangements where both parties reimburse each other for research costs, such as our collaboration agreement with Merck for the co-development of RNAi therapeutics for the treatment of ocular diseases, in which both parties reimburse each other for 50% of the costs incurred, as defined by the agreement, we follow EITF Issue No. 01-9, Accounting for Consideration Given by a Vendor to a Customer (Including a Reseller of the Vendor's Products), or EITF 01-9, in determining the proper accounting for amounts owed to Merck in reimbursement for our portion of Merck's costs under the agreement. In accordance with EITF 01-9, our policy is to record revenues equal to the amount we are due to receive for costs incurred under the agreement less amounts reimbursable to the other party during the same accounting period unless both of the following conditions exist:

- we receive a separable and identifiable benefit in exchange for the payments made to the other party under the arrangement and
- we can reasonably estimate the fair value of the benefit received.

We have recorded revenues under our collaboration agreement with Merck for the co-development of RNAi therapeutics for the treatment of ocular diseases equal to $2.5 million in 2005 and $1.8 million in 2004, which represents amounts that we have earned for costs incurred under this agreement. As the above conditions do not exist with regard to this agreement, we have recorded a reduction to our revenues of $0.3 million in 2005 and 2004, which represents amounts owed to Merck for reimbursement of 50% of the costs incurred by Merck under the agreement.

Novartis

In consideration for rights granted to Novartis under the collaboration and license agreement, Novartis made an up-front payment of $10.0 million to us in October 2005, to partly reimburse prior costs incurred by us to develop *in vivo* RNAi technology. In addition, the collaboration and license agreement includes terms under which Novartis will provide us with research funding and milestone payments as well as royalties on annual net sales of products resulting from the collaboration and license agreement. We have recorded as deferred revenue the non-refundable $10.0 million up-front payment and $6.4 million premium that represents the difference between the purchase price and the closing price of our common stock on the date of the stock purchase from Novartis. In addition to these payments, research funding and certain milestone payments will be amortized into revenue using the proportional performance method over the estimated duration of the Novartis agreement or ten years. Under this model, we will estimate the level of effort to be expended over the term of the agreement and recognize revenue based on the lesser of the amount calculated based on the proportional performance of total expected revenue or the amount of non-refundable payments earned.

We believe the estimated term of the Novartis agreement includes the three-year term of the agreement, two one-year extensions at the election of Novartis and limited support as part of a technology transfer until the fifth anniversary of the termination of the agreement. Therefore, an expected term of ten years is used in the proportional performance model. We will evaluate the expected term when new information is known that could affect our

estimate. In the event our period of involvement is different than we estimated, revenue recognition will be adjusted on a prospective basis. We recognized approximately $0.7 million in revenues during 2005 under our Novartis agreement.

Management has discussed the development, selection and disclosure of these critical accounting policies with the audit committee of our board of directors.

Results of Operations

The following data summarizes the results of our operations for the periods indicated, in thousands:

	Year Ended December 31,		
	2005	2004	2003
Net revenues	$ 5,716	$ 4,278	$ 176
Operating expenses	49,188	36,542	25,233
Loss from operations	(43,472)	(32,264)	(25,057)
Net loss	$(42,914)	$(32,654)	$(25,033)

Discussion of Results of Operations for 2005 and 2004

Revenues

The following table summarizes our total consolidated revenues for the periods indicated, in thousands:

	Year Ended December 31,	
	2005	2004
Net revenues recorded from collaboration agreements with Merck	$3,579	$4,066
Revenues recorded from collaboration agreement with CFFT	800	—
Revenues recorded from collaboration agreement with Novartis	746	—
Revenues recorded from InterfeRx license agreements	350	—
Other revenues	241	212
Total revenues recorded	$5,716	$4,278

Under our October 2005 collaboration and license agreement with Novartis, we received an up-front payment totaling $10.0 million in consideration for rights granted to Novartis under our collaboration and to partly reimburse prior costs incurred by us to develop *in vivo* RNAi technology. In addition, on October 12, 2005, Novartis purchased approximately 5.3 million shares at a purchase price of $11.11 per share for an aggregate purchase price of approximately $58.5 million. The closing price of our common stock on the date of purchase was $9.90. We recorded the difference between the purchase price and the closing price of $6.4 million as deferred revenue. We recognized revenues of $0.7 million under our Novartis collaboration during 2005.

Under our September 2003 collaboration and license agreement with Merck, we have received up-front and license payments which have been deferred and are being recognized as revenue over six years, the estimated period of performance under this agreement. In September 2003, we received a $2.0 million payment and, in both September 2004 and September 2005, we received additional payments of $1.0 million. We recognized revenues of $0.9 million, $0.6 million and $0.1 million from the amortization of these payments in 2005, 2004 and 2003, respectively.

In December 2004, we achieved a scientific milestone, as defined by this agreement, resulting in a $2.0 million milestone payment from Merck. In connection with the achievement of this scientific milestone, Merck made a $5.0 million equity investment in our common stock. The purchase price of this common stock, as defined by the agreement, was determined based on the average trading price of our common stock during the twenty days prior to the purchase, which was $7.04. The price of our common stock on the date of the purchase was $7.40 and resulted in an actual value of $5.3 million for the common stock issued to Merck. As a result, we recorded a reduction of $0.3 million to the revenue recorded from Merck during 2004.

In June 2004, we entered into an additional collaboration and license agreement with Merck for the co-development of RNAi therapeutics for the treatment of ocular diseases. Under the terms of the agreement, we received a $2.0 million license fee from Merck, as well as $1.0 million representing reimbursement of prior research and development costs, which we incurred on our pre-existing AMD program. These amounts are being amortized into revenues over the estimated period of performance under the collaboration agreement of eight years. As such, we recorded revenues of $0.5 million in 2005 and $0.2 million in 2004 from the amortization of these payments. In addition to up-front and milestone payments, this agreement provides for the sharing of research costs incurred under this agreement. We recorded net revenues of $2.2 million in 2005 and $1.5 million in 2004 from these cost sharing activities.

In March 2005, we entered into a collaboration agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, to investigate the potential for RNAi therapeutics to treat CF. Under this collaboration, CFFT provided us with an initial payment of $0.5 million and a milestone payment of $0.3 million and may make additional payments totaling an aggregate of $0.7 million in the event that certain scientific milestones are achieved. In addition to funding, CFFT will provide us with access to certain scientific resources to support our siRNA discovery and development efforts. If the discovery and development efforts under this collaboration result in the identification of siRNAs that are candidates for further development, the parties may negotiate a mutually agreeable support arrangement for further phases of development. In the event that we develop a marketable therapeutic for the treatment of CF, we will be required to pay CFFT pre-determined payments. We recorded revenues of $0.8 million in 2005 under this collaboration.

In addition to our collaboration agreements, under our InterfeRx program, we have licensed our intellectual property to others for the development and commercialization of RNAi therapeutics in narrowly defined therapeutic areas in which we are not currently engaged. We have also granted licenses to our intellectual property to others for the development and commercialization of research reagents and services. We expect these programs to provide revenues from license fees and royalties on sales by the licensees, subject to limitations under our agreement with Novartis. Under existing programs, we recognized revenues of $0.4 million in 2005.

Deferred revenue of $20.8 million at December 31, 2005 represents payments received from our collaborators pursuant to our license agreements with them which we have yet to earn pursuant to our revenue recognition policy.

For the foreseeable future, we expect our revenues to continue to be derived primarily from strategic alliances, collaborations and licensing activities.

Operating Expenses

The following tables summarize our operating expenses for the periods indicated, in thousands and as a percentage of total expenses, together with the changes in thousands and percentages:

	2005	% of Total Operating Expenses	2004	% of Total Operating Expenses	Increase $	Increase %
Research and development	$35,319	72%	$24,603	67%	$10,716	44%
General and administrative	13,869	28%	11,939	33%	$ 1,930	16%
Total operating expenses	$49,188	100%	$36,542	100%	$12,646	35%

Research and development

The following tables summarize the components of our research and development expenses for the periods indicated, in thousands and as a percentage of total research and development expenses together with the changes in thousands and percentages:

	2005	% of Expense Category	2004	% of Expense Category	Increase $	Increase %
Research and development						
Compensation and related	$ 6,895	20%	$ 5,925	24%	$ 970	16%
External services	9,461	27%	3,489	14%	5,972	171%
License and patent fees	6,904	20%	5,833	24%	1,071	18%
Lab supplies and materials	3,672	10%	3,057	12%	615	20%
Facilities-related expenses	4,668	13%	3,055	12%	1,613	53%
Stock-based compensation	2,431	7%	2,087	9%	344	16%
Other	1,288	3%	1,157	5%	131	11%
Total research and development	$35,319	100%	$24,603	100%	$10,716	44%

During the year ended December 31, 2005, our research and development expenses have increased due to the expansion of our research and development organization in support of the growth of our programs.

As indicated by the table above, the most significant increase in our research and development expenses in 2005 was external services. External services includes pre-clinical expenses, clinical expenses and consulting expenses related to the development of our RSV program and our AMD program, for which development was suspended in September 2005 based on changing clinical development and commercial factors. License and patent fees for 2005 included $3.7 million in payments to certain entities as a result of the Novartis agreement as well as a $2.1 million non-cash charge in the second quarter of 2005 resulting from the issuance of 270,000 shares of our common stock in connection with the June 2005 amendment to our license agreements with Garching Innovation GmbH. Our facilities-related research and development expenses increased in 2005 due to the occupation of our new facility for all of 2005 compared to only half of 2004. We expect to continue to devote a substantial portion of our resources to research and development expenses.

Prior to July 1, 2004, we did not track any of our research and development costs or our personnel and personnel-related costs on a project-by-project basis, because the majority of our efforts were focused on the development of capabilities associated with our product platform rather than on specific projects. In July 2004, we began work under our agreement with Merck for the co-development of RNAi ocular therapeutics. This agreement is a cost sharing arrangement whereby each party reimburses the other for 50% of the costs incurred under the project, as defined by the agreement. Costs reimbursed under the agreement include certain direct external costs and a negotiated full-time equivalent labor rate for the actual time worked on the project. As a result, we began tracking direct external costs attributable to this agreement and the actual time worked by our employees on this agreement in July 2004. However, a significant portion of our research and development expenses are not tracked on a project-by-project basis. Direct external costs incurred under our agreement with Merck for the co-development of RNAi ocular therapeutics were $0.3 million in 2005 and $0.9 million in 2004 as well as approximately $0.3 million in 2005 and $0.3 million in 2004 billed to us by Merck, which is recorded as a reduction of revenue. In addition, as of December 31, 2005, the majority of our research programs were in the pre-clinical phase, meaning that we were conducting formulation, efficacy, pharmacology and/or toxicology testing of compounds in animal models and/or biochemical assays. We initiated human clinical trials for our proprietary RNAi therapeutic for the treatment of patients with RSV in late 2005.

General and administrative

The following tables summarize the components of our general and administrative expenses for the periods indicated, in thousands and as a percentage of total general and administrative expenses, together with the changes in thousands and percentages:

	2005	% of Expense Category	2004	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
General and administrative						
Compensation and related	$ 3,339	24%	$ 3,316	28%	$ 23	1%
Consulting and professional services	3,780	27%	2,891	24%	889	31%
Facilities related	1,893	14%	2,135	18%	(242)	(11)%
Stock-based compensation	2,166	16%	2,019	17%	147	7%
Insurance	616	4%	388	3%	228	59%
Other	2,075	15%	1,190	10%	885	74%
Total general and administrative	$13,869	100%	$11,939	100%	$1,930	16%

As indicated in the table above, the most significant increase in general and administrative expenses in 2005 was an increase in consulting and professional services, which was due primarily to increases in expenses associated with business development activities and Sarbanes-Oxley compliance efforts. Increased insurance costs in 2005 were a result of our operation for a full year as a publicly traded company.

Interest income, interest expense and other

Interest income was $1.5 million in 2005 compared to $0.5 million in 2004. The increase was due to our higher average cash, cash equivalent and marketable securities balances in 2005, as well as higher average interest rates.

Interest expense was $1.0 million in 2005 compared to $0.7 million in 2004. Interest expense for 2005 is the result of increased borrowings under our line of credit with Lighthouse used to finance capital equipment purchases. We expect that our interest expense will increase as we finance additional capital expenditures.

Other expense was less than $0.1 million in 2005 compared to $0.2 million in 2004. This change is due primarily to realized foreign currency gains in 2005, partially offset by foreign currency losses and expenses associated with an adjustment to our deferred tax asset.

Discussion of Results of Operations for 2004 and 2003

Revenues

The following table summarizes the payments received by us under our strategic research collaboration agreements with Merck as well as our total consolidated revenues in the periods indicated, in thousands:

	Year Ended December 31, 2004	Year Ended December 31, 2003
Net revenues recorded from collaboration agreements with Merck	$4,066	$111
Other revenues	212	65
Total revenues recorded	$4,278	$176

We received a $2.0 million license fee from our first agreement with Merck in September 2003, which has been deferred and is being recognized as revenue over six years, the estimated period of performance under the collaboration agreement. In September 2004, we received an additional license fee of $1.0 million from Merck related to this agreement. We recognized revenues of $0.6 million and $0.1 million from the amortization of these payments in 2004 and 2003, respectively. The increase in these revenues is due to a full year of amortization of the payment received in September 2003 and the amortization of the additional payment received in September 2004.

In December 2004, we achieved a scientific milestone, as defined by this agreement, resulting in a $2.0 million milestone payment from Merck. In connection with the achievement of this scientific milestone, Merck made a $5.0 million equity investment in our common stock. The purchase price of this common stock, as defined by the agreement, was determined based on the average trading price of our common stock during the twenty days prior to the purchase, which was $7.04. The price of our common stock on the date of the purchase was $7.40 and resulted in an actual value of $5.3 million for the common stock issued to Merck. As a result, we recorded a reduction of $0.3 million to the revenue recorded from Merck.

In June 2004, we entered into an additional collaboration and license agreement with Merck for the co-development of RNAi therapeutics for the treatment of ocular diseases. Under the terms of the agreement, we received a $2.0 million license fee from Merck as well as $1.0 million representing reimbursement of prior research and development costs which we incurred on our AMD program targeting vascular endothelial growth factor, or VEGF. These amounts are being amortized into revenues over the estimated period of performance under the collaboration agreement of six years. As such, we recorded $0.2 million of revenues in 2004 from the amortization of these payments. In addition to up-front and milestone payments, our collaboration agreement with Merck related to RNAi therapeutics for ocular diseases provides for the sharing of costs incurred under this agreement. In 2004, we recorded net revenues of $1.5 million from these cost sharing activities related to the AMD program.

Operating Expenses

The following table summarizes our operating expenses for the periods indicated, in thousands and as a percentage of total expenses:

	2004	% of Total Operating Expenses	2003	% of Total Operating Expenses	Increase (Decrease) $	Increase (Decrease) %
Research and development	$24,603	67%	$13,097	52%	$11,506	88%
General and administrative	11,939	33%	7,527	30%	4,412	59%
Purchased in-process research and development	—	—	4,609	18%	(4,609)	(100)%
Total operating expenses	$36,542	100%	$25,233	100%	$11,309	45%

Research and development

The following table summarizes the most significant components of our research and development expenses for the periods indicated, in thousands and as a percentage of total research and development expenses and provides the changes in thousands and percentages:

	2004	% of Expense Category	2003	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
Research and development						
Compensation and related	$ 5,925	24%	$ 3,043	23%	$ 2,882	95%
External services	3,489	14%	2,153	17%	1,336	62%
License fees	5,833	24%	1,720	13%	4,113	239%
Lab supplies and materials	3,057	12%	1,628	12%	1,429	88%
Facilities-related expenses	3,055	12%	1,197	9%	1,858	155%
Stock-based compensation	2,087	9%	2,833	22%	(746)	(26)%
Other	1,157	5%	523	4%	634	121%
Total research and development	$24,603	100%	$13,097	100%	$11,506	88%

During the year ended December 31, 2004, our research and development expenses increased due to the expansion of our research and development organization in support of the growth of our programs.

As indicated by the table above, the most significant increase in our research and development expenses in 2004 was additional license fees. This increase was primarily due to $5.5 million in license fees incurred in connection with our license agreement with Isis. In addition, our research and development expenses increased in 2004 due to increased compensation and related costs as a result of the timing and size of the expansion of our research and development organization, which increased from 42 employees at December 31, 2003 to 51 at December 31, 2004. In addition to the increase in employees in our research organization, we improved our research infrastructure by moving into new facilities during 2004, which resulted in increased facilities related costs. The expansion of our research organization was in support of both the growth of existing research programs such as AMD and PD as well the addition of new research programs initiated during 2004, including RSV. This growth resulted in increased external service costs including consulting and contracted research with third parties.

General and administrative

The following table summarizes the most significant components of our general and administrative expenses for the periods indicated, in thousands and as a percentage of total general and administrative expenses and provides the changes in thousands and percentages:

	2004	% of Expense Category	2003	% of Expense Category	Increase $	Increase %
General and administrative						
Compensation and related	$ 3,316	28%	$2,490	33%	$ 826	33%
Consulting and professional services	2,891	24%	2,816	38%	75	3%
Facilities related	2,135	18%	682	9%	1,453	213%
Stock-based compensation	2,019	17%	623	8%	1,396	224%
Insurance	388	3%	35	0%	353	1,009%
Other	1,190	10%	881	12%	309	35%
Total general and administrative	$11,939	100%	$7,527	100%	$4,412	59%

As indicated in the table above, the most significant increase in general and administrative expenses in 2004 was increased facilities related costs as a result of our relocation into our new headquarters in Cambridge, Massachusetts in April 2004. Another significant component of the increase in general and administrative expenses was in non-cash stock-based compensation, which increased as a result of the amortization of additional deferred compensation recorded as a result of stock option grants to employees prior to our initial public offering.

Purchased in-process research and development

In July 2003, in connection with our acquisition of Alnylam Europe, we allocated $4.6 million of the purchase price to purchased in-process research and development, which we recorded as an expense in our consolidated statement of operations in 2003. During 2004, we did not incur any such charges.

Interest income, interest expense and other

Interest income increased to $0.5 million in 2004 from $0.2 million in 2003. This increase was due to our higher average cash, cash equivalent and marketable securities balances in 2004, which was primarily a result of the net proceeds of approximately $29.9 million from our initial public offering in June 2004 and from the issuance of $10.0 million of our Series D preferred stock in March 2004.

Interest expense increased to $0.7 million in 2004 from $0.1 million in 2003. This increase was due primarily to our establishment of a $10.0 million equipment line of credit in March 2004. During 2004, we drew down approximately $7.2 million under this line of credit.

Other expenses increased to $0.2 million in 2004 from less than $0.1 million in 2003. This increase is due primarily to realized foreign currency losses as a result of the increase in the conversion rate of the Euro against the U.S. Dollar.

Liquidity and Capital Resources

The following table summarizes our cash flow activities for the periods indicated, in thousands:

	Year Ended December 31,		
	2005	2004	2003
Net loss	$(42,914)	$(32,654)	$(25,033)
Adjustments to reconcile net loss to net cash used in operating activities	9,672	9,602	9,299
Changes in operating assets and liabilities	16,757	3,482	2,906
Net cash used in operating activities	(16,485)	(19,570)	(12,828)
Net cash used in investing activities	(40,418)	(34,595)	(3,240)
Net cash provided by financing activities	52,617	50,977	23,708
Effect of exchange rate on cash	(229)	267	76
Net (decrease) increase in cash and cash equivalents	(4,515)	(2,921)	7,716
Cash and cash equivalents, beginning of period	20,272	23,193	15,477
Cash and cash equivalents, end of period	$ 15,757	$ 20,272	$ 23,193

We commenced operations in June 2002 and since our inception, we have generated significant losses. As of December 31, 2005, we had an accumulated deficit of $105.9 million. As of December 31, 2005, we had cash, cash equivalents and marketable securities of $80.0 million, compared to cash, cash equivalents and marketable securities of $46.0 million as of December 31, 2004. This cash balance does not include approximately $62.3 million of net proceeds from our follow-on public offering of approximately 5.1 million shares of common stock on January 31, 2006. We invest primarily in cash equivalents, U.S. government obligations, high-grade corporate notes and commercial paper. Our investment objectives are primarily, to assure liquidity and preservation of capital and, secondarily, to obtain investment income. All of our investments in debt securities are recorded at fair value and are available for sale. Fair value is determined based on quoted market prices.

Operating activities

We have required, and expect to continue to require for the foreseeable future, significant amounts of cash to fund our operating activities as a result of net losses since our inception. This trend continued during 2005 as our net loss increased for the year ended December 31, 2005 as compared to year ended December 31, 2004 due to continued funding of our operations, including activities leading up to our recent initiation of two Phase I clinical trials to evaluate in healthy volunteers the safety, tolerability, and pharmacokinetics of ALN-RSV01. Cash used in operating activities is adjusted for non-cash items to reconcile net loss to net cash used in operating activities. These non-cash adjustments primarily consist of stock-based compensation, depreciation, amortization and, in year ended December 31, 2005, non-cash license expense. Non-cash stock-based compensation increased due to the increase of the fair value of stock options variable accounting, the issuance of additional stock options with variable accounting and the vesting of a stock option upon the execution of our agreements with Novartis. In addition, in 2005 we recorded a $2.1 million non-cash license expense related to the June 2005 amendment of our license agreement with Garching, which resulted in the issuance of 270,000 shares of our common stock in July 2005. Depreciation expense has increased as a result of additional property and equipment we have acquired to expand our research capacity and support the growth of our infrastructure, mainly in our new corporate headquarters and research facilities in Cambridge, Massachusetts, which we moved into in April 2004. Amortization expense is associated with intangible assets recorded in connection with our acquisition of Ribopharma AG, now Alnylam Europe AG, in July 2003. In addition, changes in our operating assets and liabilities have affected our net cash used in operating activities since our inception. The increase is primarily due to the up-front payment from Novartis of $10.0 million as well as the $6.4 million stock purchase premium from Novartis which were recorded as deferred revenue. This increase was partially offset due to our January 2005 payment of $2.0 million to Isis under our March 2004 license agreement.

Investing activities

In 2004, we began investing the proceeds from our initial public offering and other equity financing proceeds in marketable securities, which was our most significant investing activity during this period. In addition, we made significant investments in property and equipment during 2004 due to the expansion of our operations into new corporate headquarters and research facilities in Cambridge, Massachusetts in April 2004. These activities resulted in a significant use of our cash in 2004. As our move into these facilities was completed in April 2004, we have experienced a significant decline in purchases of property and equipment. While we continue to purchase property and equipment to support the growth of our research and overall operations, these purchases were considerably lower in 2005 as compared to purchases made in 2004. In 2005, we increased our sales of marketable securities to fund our operating activities, which resulted in a net inflow of cash from investing activities.

On March 26, 2004, we entered into an agreement with Perini Building Company, Inc., or Perini, for the build out of our new facility in Cambridge, Massachusetts. The contract contained a guaranteed maximum price of $5.6 million, $5.0 million of which was paid by us in 2004 and $0.3 million was paid on our behalf directly to Perini by our landlord in 2004. These payments represent payment in full through the completion of the project. As part of the lease agreement that we entered into with the landlord of this facility, the landlord agreed to reimburse us for up to approximately $3.0 million of certain of the costs of the tenant improvements. Through December 31, 2005, we received approximately $3.0 million from the landlord, which represent all of the reimbursements due to us under the agreement. These reimbursements have been recorded as long-term deferred rent in our balance sheet and are being amortized against rent expense over the remaining lease term.

Financing activities

Since our inception, we have funded our operations primarily through the sale of equity securities. Through 2005, we raised approximately $54.8 million in net proceeds from the sale of redeemable convertible preferred stock and approximately $93.7 million from the sale of common stock, including $29.9 million from the sale of 5.75 million shares of our common stock in our initial public offering, which was completed in June 2004, $58.4 million from the sale of approximately 5.3 million shares of our common stock to Novartis, which was completed in October 2005.

Certain of our sales of equity securities have been in connection with our strategic collaboration and licensing agreements, including with Novartis, as described above. In connection with our March 2004 collaboration and license agreement with Isis, Isis purchased 1,666,667 shares of our Series D preferred stock for $10.0 million which were converted into 877,193 shares of our common stock upon the closing of our initial public offering in June 2004. In September 2003, we entered into a collaboration and license agreement with Merck for the development of RNAi-based technology and therapeutics. In connection with this agreement, Merck purchased 1,000,000 shares of our Series C preferred stock for $5.0 million, which were converted into 526,315 shares of our common stock upon the closing of our initial public offering, and 710,273 shares of our common stock for $5.0 million in December 2004.

In addition to sales of equity securities, we have financed a portion of our property and equipment purchases through the establishment of equipment lines of credit. In December 2002, we established a $2.5 million equipment line of credit under which we drew down approximately $2.1 million in 2003, of which $1.8 million was repaid in March 2004. In March 2004, we entered into an equipment line of credit with Lighthouse Capital Partners to finance leasehold improvements and equipment purchases of up to $10.0 million. The outstanding principal bears interest at a fixed rate of 9.25%, except for the drawdown made in December 2005 which bears interest at a fixed rate of 10.25%, maturing at various dates through December 2009. We were required to make interest-only payments on all draw-downs made during the period from March 26, 2004 through June 30, 2005, at which point all draw-downs began to be repaid over 48 months. The borrowings are collateralized by the assets financed. At December 31, 2005, we had an outstanding principal balance of $7.4 million under this facility. The terms of the Lighthouse agreement include covenants which limit our ability to sell or transfer certain assets or businesses. In June 2005, we entered into an amendment to our agreement with Lighthouse to extend the drawdown period of the loan to December 31, 2005.

Based on our current operating plan, we believe that our existing resources, together with the cash we expect to generate under our current alliances, including our October 2005 alliance with Novartis and our follow-on offering of common stock completed in January 2006 will be sufficient to fund our planned operations beyond the end of

2007, during which time we expect to extend the capabilities of our technology platform, further the development of our products, conduct clinical trials and continue to prosecute patent applications and otherwise build and maintain our patent portfolio. However, we may require significant additional funds earlier than we currently expect in order to develop and commence clinical trials for any product candidates.

We may seek additional funding through collaborative arrangements and public or private financings. Additional funding may not be available to us on acceptable terms or at all. In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our existing stockholders may result. If we are unable to obtain funding on a timely basis, we may be required to significantly curtail one or more of our research or development programs. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies or product candidates that we would otherwise pursue.

Even if we are able to raise additional funds in a timely manner, our future capital requirements may vary from what we expect and will depend on many factors, including the following:

- our progress in demonstrating that siRNAs can be active as drugs;
- our ability to develop relatively standard procedures for selecting and modifying siRNA drug candidates;
- progress in our research and development programs, as well as the magnitude of these programs;
- the timing, receipt, and amount of milestone and other payments, if any, from present and future collaborators, if any;
- our ability to establish and maintain additional collaborative arrangements;
- the resources, time and costs required to successfully initiate and complete our pre-clinical and clinical trials, obtain regulatory approvals, protect our intellectual property and obtain and maintain licenses to third-party intellectual property;
- the cost of preparing, filing, prosecuting, maintaining, and enforcing patent claims; and
- the timing, receipt and amount of sales and royalties, if any, from our potential products.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements or relationships with unconsolidated entities or financial partnerships, such as entities often referred to as structured finance or special purpose entities.

Contractual Obligations and Commitments

Set forth below is a description of our contractual cash obligations as of December 31, 2005, in thousands.

	Payments Due by Period				
Contractual Obligations	2006	2007 and 2008	2009 and 2010	After 2010	Total
Operating lease obligations	$2,231	$ 4,787	$4,436	$1,663	$13,117
Short and long-term debt	2,462	4,925	2,179	—	9,566
Fixed license payments	335	670	670	3,660	5,335
Total contractual cash obligations	$5,028	$10,382	$7,285	$5,323	$28,018

We in-license technology from a number of sources. Pursuant to these in-license agreements, we will be required to make additional payments if and when we achieve specified development and regulatory milestones.

Recently Issued Accounting Pronouncements

In December 2004, the FASB issued SFAS No. 123R, Share-Based Payment, or SFAS 123R, which revises SFAS No. 123, Accounting for Stock-based Compensation, and requires companies to expense the fair value of employee stock options and other forms of stock-based compensation. Under SFAS 123R, the most significant

change in practice would be treating the fair value of stock based payment awards that are within its scope as compensation expense in the income statement beginning on the date that a company grants the awards to employees. In April 2005, the SEC delayed the effective date of SFAS 123R to financial statements issued for the first annual period beginning after June 15, 2005. As a result, we will adopt and comply with the requirements of SFAS 123R in the three months ending March 31, 2006. We are currently assessing the impact that the adoption of this standard will have on our financial position and results of operations and the method by which we will implement this standard, however, we expect stock compensation expense to materially increase as a result of the adoption of this standard.

In May 2005, the FASB issued SFAS No. 154, Accounting Changes and Error Corrections, or SFAS No. 154. SFAS No. 154 is a replacement of APB No. 20 and FASB Statement No. 3. SFAS No. 154 provides guidance on the accounting for and reporting of accounting changes and error corrections. It establishes retrospective application as the required method for reporting a change in accounting principle. SFAS No. 154 provides guidance for determining whether retrospective application of a change in accounting principle is impracticable and for reporting a change when retrospective application is impracticable. The reporting of a correction of an error by restating previously issued financial statements is also addressed by SFAS No. 154. SFAS No. 154 is effective for accounting changes and corrections of errors made in fiscal years beginning after December 15, 2005. We do not expect the adoption of SFAS No. 154 will have a material impact on our financial position or results of operations.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As part of our investment portfolio, we own financial instruments that are sensitive to market risks. The investment portfolio is used to preserve our capital until it is required to fund operations, including our research and development activities. Our marketable securities consist of U.S. government obligations, corporate debt and commercial paper. All of our investments in debt securities are classified as "available-for-sale" and are recorded at fair value. Our "available-for-sale" investments are sensitive to changes in interest rates. Interest rate changes would result in a change in the net fair value of these financial instruments due to the difference between the market interest rate and the market interest rate at the date of purchase of the financial instrument. A 10% decrease in market interest rates at December 31, 2005 would impact the net fair value of such interest-sensitive financial instruments by approximately $300,000.

Our $10.0 million equipment line of credit with Lighthouse Capital Partners V, L.P. bears a fixed interest rate of prime plus 3%. As a result, any changes in the prime rate will not affect our future payments for existing debt outstanding under this line of credit.

Foreign Currency Exchange Rate Risk

We are exposed to foreign currency exchange rate risk. Our European operations are based in Kulmbach, Germany and the functional currency of these operations is the Euro. We provide periodic funding to support these operations. The amount of this funding is based upon actual expenditures incurred by our European operations and is calculated in Euros. The effect that fluctuations in the exchange rate between the Euro and the United States Dollar have on the amounts payable to fund our European operations are recorded in our consolidated statements of operations as other income or expense. We do not enter into any foreign exchange hedge contracts.

Assuming the amount of expenditures by our European operations were consistent with 2005 and the timing of the funding of these operations were to remain consistent during the remainder of 2006, a constant increase or decrease in the exchange rate between the Euro and the United States Dollar during the remainder of 2006 of 10% would result in a foreign exchange gain or loss of approximately $50,000.

The amount of our foreign currency exchange rate risk is based on many factors including the timing and size of fluctuations in the currency exchange rate between the Euro and the United States Dollar, the amount of actual expenditures incurred by our European operations and the timing and size of funding provided to our European operations from the United States.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Management's Annual Report on Internal Control Over Financial Reporting

The management of the Company is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) or 15d-15(f) promulgated under the Securities Exchange Act of 1934 as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of the assets of the Company;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the Company are being made only in accordance with authorizations of management and directors of the Company; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the Company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

The Company's management assessed the effectiveness of the Company's internal control over financial reporting as of December 31, 2005. In making this assessment, the Company's management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control-Integrated Framework.

Based on our assessment, management concluded that, as of December 31, 2005, the Company's internal control over financial reporting is effective based on those criteria.

The Company's independent registered public accounting firm has issued an audit report on our assessment of the Company's internal control over financial reporting. This report appears on page 68.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of
Alnylam Pharmaceuticals, Inc.:

We have completed an integrated audit of Alnylam Pharmaceuticals, Inc.'s 2005 consolidated financial statements and of its internal control over financial reporting as of December 31, 2005 and audits of its 2004 and 2003 financial statements in accordance with the standards of the Public Company Accounting Oversight Board (United States). Our opinions, based on our audits, are presented below.

Consolidated financial statements and financial statement schedule

In our opinion, the consolidated financial statements listed in the index appearing under Item 15(a)(1) present fairly, in all material respects, the financial position of Alnylam Pharmaceuticals, Inc. and its subsidiaries at December 31, 2005 and 2004, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2005 in conformity with accounting principles generally accepted in the United States of America. In addition, in our opinion, the financial statement schedule listed in the index appearing under Item 15(a)(2) presents fairly, in all material respects, the information set forth therein when read in conjunction with the related consolidated financial statements. These financial statements and financial statement schedule are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements and financial statement schedule based on our audits. We conducted our audits of these statements in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit of financial statements includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

Internal control over financial reporting

Also, in our opinion, management's assessment, included in Management's Annual Report on Internal Control Over Financial Reporting appearing under Item 8, that the Company maintained effective internal control over financial reporting as of December 31, 2005 based on criteria established in *Internal Control — Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO), is fairly stated, in all material respects, based on those criteria. Furthermore, in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2005, based on criteria established in *Internal Control — Integrated Framework* issued by the COSO. The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting. Our responsibility is to express opinions on management's assessment and on the effectiveness of the Company's internal control over financial reporting based on our audit. We conducted our audit of internal control over financial reporting in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. An audit of internal control over financial reporting includes obtaining an understanding of internal control over financial reporting, evaluating management's assessment, testing and evaluating the design and operating effectiveness of internal control, and performing such other procedures as we consider necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinions.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts
March 16, 2006

ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(In thousands, except share and per share amounts)

	December 31, 2005	December 31, 2004
ASSETS		
Current assets:		
Cash and cash equivalents	$ 15,757	$ 20,272
Marketable securities	64,245	25,774
Collaboration receivables	609	859
Related party notes receivable	146	310
Prepaid expenses and other current assets	1,657	966
Total current assets	82,414	48,181
Property and equipment, net	10,580	11,694
Intangible assets, net	2,491	3,405
Restricted cash	2,313	2,313
Other assets	550	514
Total assets	$ 98,348	$ 66,107
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 1,975	$ 910
Accrued expenses	3,899	3,875
Current portion of note payable	1,876	790
Deferred revenue	10,734	1,000
Total current liabilities	18,484	6,575
Deferred revenue, net of current portion	10,099	4,083
Deferred rent	2,467	2,896
Note payable, net of current portion	5,519	6,411
Total liabilities	36,569	19,965
Commitments and contingencies (Note 7)	—	—
Stockholders' equity:		
Preferred stock, $0.01 par value, 5,000,000 shares authorized and no shares issued and outstanding at December 31, 2005 and December 31, 2004	—	—
Common stock, $0.01 par value, 125,000,000 shares authorized; 26,721,149 shares issued and 26,638,255 shares outstanding as of December 31, 2005; 20,931,742 shares issued and 20,848,848 shares outstanding as of December 31, 2004	267	208
Additional paid-in capital	170,033	112,216
Deferred stock compensation	(2,460)	(3,697)
Accumulated other comprehensive (loss) income	(142)	420
Accumulated deficit	(105,919)	(63,005)
Total stockholders' equity	61,779	46,142
Total liabilities and stockholders' equity	$ 98,348	$ 66,107

The accompanying notes are an integral part of these consolidated financial statements.

ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except per share amounts)

	Year Ended December 31,		
	2005	2004	2003
Net revenues from research collaborators	$ 5,716	$ 4,278	$ 176
Cost and expenses:			
Research and development(1)	35,319	24,603	13,097
General and administrative(1)	13,869	11,939	7,527
Purchased in-process research and development	—	—	4,609
Total costs and expenses	49,188	36,542	25,233
Loss from operations	(43,472)	(32,264)	(25,057)
Other income (expense):			
Interest income	1,549	504	179
Interest expense	(969)	(661)	(127)
Other expense	(22)	(233)	(28)
Total other income (expense)	558	(390)	24
Net loss	(42,914)	(32,654)	(25,033)
Accretion of redeemable convertible preferred stock	—	(2,713)	(2,906)
Net loss attributable to common stockholders	$(42,914)	$(35,367)	$(27,939)
Comprehensive loss:			
Net loss	$(42,914)	$(32,654)	$(25,033)
Foreign currency translation adjustments	(534)	400	76
Unrealized loss on marketable securities	(28)	(56)	—
Comprehensive loss	$(43,476)	$(32,310)	$(24,957)
Net loss per common share — basic and diluted	$ (1.96)	$ (2.98)	$ (29.64)
Weighted average common shares used to compute basic and diluted net loss per common share	21,949	11,886	943
(1) Non-cash stock-based compensation expense included in these amounts are as follows:			
Research and development	$ 2,431	$ 2,087	$ 2,832
General and administrative	2,166	2,019	623
Total non-cash stock-based compensation	$ 4,597	$ 4,106	$ 3,455

The accompanying notes are an integral part of these consolidated financial statements.

ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CHANGES IN REDEEMABLE CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)

(In thousands, except share amounts)

	Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Deferred Stock Compensation	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount					
Balance at December 31, 2002	8,160,010	$ 18,084	1,342,084	$ —	$ —	$ (161)	$ —	$ (4,485)	$ (4,646)
Exercise of common stock options	—	—	44,526	—	21	—	—	—	21
Issuance of common stock in connection with acquisition of Ribopharma	—	—	864,872	—	2,066	—	—	—	2,066
Issuance of convertible preferred stock	12,906,670	34,199	—	—	260	—	—	—	260
Accretion of preferred stock	—	2,906	—	—	(2,906)	—	—	—	(2,906)
Deferred compensation related to stock options and restricted stock	—	—	—	—	7,975	(7,975)	—	—	—
Amortization of deferred compensation expense related to stock options and restricted stock	—	—	—	—	—	3,455	—	—	3,455
Foreign currency translation	—	—	—	—	—	—	76	—	76
Net loss	—	—	—	—	—	—	—	(25,033)	(25,033)
Balance at December 31, 2003	21,066,680	55,189	2,251,482	—	7,416	(4,681)	76	(29,518)	(26,707)
Adjustment to reflect change in par value of common stock (Note 8.)	—	—	—	22	(22)	—	—	—	—
Exercise of common stock options	—	—	255,075	3	165	—	—	—	168
Issuance of convertible preferred stock	1,666,667	10,557	—	—	833	—	—	(833)	—
Accretion of preferred stock	—	1,880	—	—	(1,880)	—	—	—	(1,880)
Repurchase of restricted stock	—	—	(82,890)	(1)	1	—	—	—	—
Deferred compensation related to stock options and restricted stock	—	—	—	—	3,056	(3,056)	—	—	—
Amortization of deferred compensation expense related to stock options and restricted stock	—	—	—	—	65	4,040	—	—	4,105
Conversion of redeemable convertible preferred stock into common stock upon initial public offering	(22,733,347)	(67,626)	11,964,908	120	67,506	—	—	—	67,626
Issuance of common stock upon initial public offering, net of offering costs of $4,616	—	—	5,750,000	57	29,827	—	—	—	29,884
Issuance of common stock pursuant to collaboration agreement	—	—	710,273	7	5,249	—	—	—	5,256
Foreign currency translation	—	—	—	—	—	—	399	—	399
Unrealized loss on marketable securities	—	—	—	—	—	—	(55)	—	(55)
Net loss	—	—	—	—	—	—	—	(32,654)	(32,654)
Balance at December 31, 2004	—	—	20,848,848	208	112,216	(3,697)	420	(63,005)	46,142

The accompanying notes are an integral part of these consolidated financial statements.

ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CHANGES IN REDEEMABLE CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT) — (Continued)

(In thousands, except share amounts)

	Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Deferred Stock Compensation	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount					
Exercise of common and restricted stock options and warrants	—	—	199,750	2	184	—	—	—	186
Issuance of common stock	—	—	5,589,657	57	54,273	—	—	—	54,330
Deferred compensation related to stock options and restricted stock	—	—	—	—	2,661	(2,661)	—	—	—
Amortization of deferred compensation expense related to stock options and restricted stock	—	—	—	—	699	3,898	—	—	4,597
Foreign currency translation	—	—	—	—	—	—	(534)	—	(534)
Unrealized loss on marketable securities	—	—	—	—	—	—	(28)	—	(28)
Net loss	—	—	—	—	—	—	—	(42,914)	(42,914)
Balance at December 31, 2005	—	—	26,638,255	$267	$170,033	$(2,460)	$(142)	$(105,919)	$ 61,779

The accompanying notes are an integral part of these consolidated financial statements.

ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,		
	2005	2004	2003
Cash flows from operating activities:			
Net loss	$(42,914)	$(32,654)	$(25,033)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	3,119	2,444	838
Loss on disposal of equipment	—	49	—
Non-cash stock-based compensation	4,597	4,106	3,455
Series B preferred stock issued for Garching license	—	—	397
Charge for purchased in-process research and development	—	—	4,609
Proceeds from landlord for tenant improvements	—	3,003	—
Realized foreign currency (gains)	(137)	—	—
Non-cash license expense	2,093	—	—
Changes in operating assets and liabilities, net of effects of acquisition:			
Collaboration receivables	243	(859)	—
Prepaid expenses and other assets	(256)	(637)	(558)
Accounts payable	1,025	(615)	794
Accrued expenses	(12)	2,399	781
Deferred revenue	15,757	3,194	1,889
Net cash used in operating activities	(16,485)	(19,570)	(12,828)
Cash flows from investing activities:			
Purchases of property and equipment	(1,947)	(9,006)	(3,119)
Proceeds from sale of equipment	—	185	—
Purchases of marketable securities	(70,882)	(33,499)	—
Sales of marketable securities	32,411	7,725	—
Acquisition of Ribopharma AG, net of cash acquired	—	—	(121)
Net cash used in investing activities	(40,418)	(34,595)	(3,240)
Cash flows from financing activities:			
Proceeds from issuance of common stock, net of issuance costs	52,423	35,308	21
Proceeds from issuance of preferred stock, net of issuance costs	—	10,000	27,459
Proceeds from bank debt	1,037	7,201	2,098
Repayments of bank debt	(843)	(1,859)	(239)
Repayment of debt assumed in acquisition	—	—	(2,964)
Increase (decrease) in restricted cash	—	373	(2,667)
Deferred financing costs incurred in connection with the equipment line of credit	—	(46)	—
Net cash provided by financing activities	52,617	50,977	23,708
Effect of exchange rate on cash	(229)	267	76
Net (decrease) increase in cash and cash equivalents	(4,515)	(2,921)	7,716
Cash and cash equivalents, beginning of period	20,272	23,193	15,477
Cash and cash equivalents, end of period	$ 15,757	$ 20,272	$ 23,193

ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF STATEMENTS OF CASH FLOWS — (Continued)
(In thousands)

	Year Ended December 31,		
	2005	2004	2003
Supplemental disclosure of cash flows			
Cash paid for interest	$ 633	$ 487	$ 503
Supplemental disclosure of non-cash financing activities			
Common stock issued to Garching in 2005	$ 2,093	$ —	$ —
Fair value of warrant issued in connection with equipment line of credit included as deferred financing costs	—	557	—
Conversion of redeemable convertible preferred stock into common stock	—	67,626	—
Accretion of redeemable convertible preferred stock	—	2,713	2,906
Series B preferred stock issued to Garching in 2003 for a license in 2002 included in accrued expenses	—	—	2,205
Conversion of note payable and accrued interest into Series B preferred stock	—	—	4,795
Beneficial conversion feature on issuance of Series A preferred stock	—	—	260
Acquisition of Ribopharma AG			
Fair value of assets acquired	$ —	$ —	$ 12,256
Assumed liabilities	—	—	(8,390)
Cash paid	—	—	(1,500)
Acquisition costs incurred	—	—	(419)
Fair value of common stock issued	$ —	$ —	$ 1,947

The accompanying notes are an integral part of these consolidated financial statements.

1. NATURE OF BUSINESS

Alnylam Pharmaceuticals, Inc. (the "Company" or "Alnylam") commenced operations on June 14, 2002 as a biopharmaceutical company seeking to develop and commercialize new drugs that work through a recently discovered system in cells known as RNA interference, or RNAi. Alnylam is focused on discovering, developing and commercializing RNAi therapeutics by establishing strategic alliances with leading pharmaceutical companies, establishing and maintaining a strong intellectual property position in the RNAi field and generating revenues through licensing agreements. The Company has devoted substantially all of its efforts to business planning, research and development, acquiring intellectual property rights, recruiting management and technical staff, and raising capital.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The Company comprises three entities, Alnylam Pharmaceuticals, Inc. (the parent company) and two subsidiaries (Alnylam U.S., Inc. and Alnylam Europe AG). Alnylam Pharmaceuticals, Inc. is a Delaware corporation that was formed on May 8, 2003 and was formerly called Alnylam Holding Co. Alnylam U.S. is also a Delaware corporation that was formed on June 14, 2002 and was previously called Alnylam Pharmaceuticals, Inc. On July 31, 2003, Alnylam Pharmaceuticals, Inc. (the parent company) and Alnylam U.S., Inc. were reorganized and Alnylam U.S., Inc. became a wholly owned subsidiary of Alnylam Pharmaceuticals, Inc. (the parent company). Since Alnylam U.S., Inc. and Alnylam Pharmaceuticals, Inc. were under common control and Alnylam Pharmaceuticals, Inc. (the parent company) did not have independent operations prior to the reorganization, the combination of the two entities did not result in a new basis of accounting.

Principles of Consolidation

The accompanying condensed consolidated financial statements reflect the operations of the Company and its wholly-owned subsidiaries Alnylam U.S., Inc. and Alnylam Europe AG. All significant intercompany accounts and transactions have been eliminated.

Reclassifications

Certain reclassifications have been made to prior years' financial statements to conform to the 2005 presentation.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States of America requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Concentrations of Credit Risk and Significant Customers

Financial instruments which potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and marketable securities. As of December 31, 2005 and 2004, substantially all of the Company's cash, cash equivalents and marketable securities were invested in money market mutual funds, commercial paper, corporate notes and government securities through two highly rated financial institutions.

To date, the Company's revenue has been generated from primarily Merck and Novartis, who owned approximately 4.6% and 19.8% of the Company's outstanding common stock as of December 31, 2005. In

2005 the Company had significant revenue from Merck and Novartis, which accounted for 63% and 13%, respectively, of the Company's total revenue. In 2004 and 2003, the Company had significant revenue from only Merck, which accounted for 95% and 63% of revenues recorded, respectively. Receivables from Novartis and Merck represented approximately 72% and 28%, respectively, of the Company's collaboration receivables balance at December 31, 2005. All amounts included in collaboration receivables at December 31, 2004 were due from Merck. Deferred revenue from Novartis and Merck represented approximately 77% and 23%, respectively, of the Company's deferred revenue balance at December 31, 2005. All amounts included in deferred revenue at December 31, 2004 were related to Merck.

Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, which include cash equivalents, collaboration receivable, accounts payable, accrued expenses and notes payable, approximate their fair values at December 31, 2005 and 2004. During 2004, the Company began investing a portion of its available cash in marketable securities which have maturities of greater than one year. The Company classifies these investments as current assets as they are available, if needed, to fund the Company's current operations. At December 31, 2005, the Company had no investments with maturities of greater than one year classified as short-term in its balance sheet. Unrealized gains or losses are included as a component of accumulated other comprehensive income, included in stockholders' equity in the consolidated balance sheets. The following table summarizes the Company's marketable securities at December 31, 2005, and 2004 in thousands:

	December 31, 2005			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Commercial paper	$ 2,024	$ 1	$ —	$ 2,025
Asset backed securities due within one year	14,752	—	(16)	14,736
Corporate notes due within one year	47,552	—	(68)	47,484
Total	$64,328	$ 1	$(84)	$64,245

	December 31, 2004			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Commercial paper	$ 2,838	$—	$ (1)	$ 2,837
Corporate notes due within one year	14,658	—	(33)	14,625
Corporate notes due in one to two years	4,942	—	(15)	4,927
Government securities	3,391	—	(6)	3,385
Total	$25,829	$—	$(55)	$25,774

Revenue Recognition

The Company recognizes revenue in accordance with the Securities and Exchange Commission's ("SEC") Staff Accounting Bulletin No. 104, Revenue Recognition in Financial Statements. The Company has entered into collaboration agreements with Merck & Co. ("Merck") and Novartis Pharma AG and its affiliate, Novartis Institutes for BioMedical Research, Inc. (collectively "Novartis") (Note 12). Revenues from these collaboration agreements may include nonrefundable license fees, milestones, research and development funding, cost reimbursements and royalties. When evaluating multiple element arrangements, the Company considers whether the components of the arrangement represents separate units of accounting as defined in Emerging Issues Task Force ("EITF") Issue No. 00-21, *Revenue Arrangements with Multiple Deliverables* ("EITF 00-21"). Application of these standards

requires subjective determinations and requires management to make judgments about the value of the individual elements and whether it is separable from the other aspects of the contractual relationship. Nonrefundable license fees are recognized as revenue as the Company performs under the collaboration agreements. Where the Company's level of effort is relatively constant over the performance period, the Company recognizes total fixed or determined contract revenues on a straight-line basis over the estimated period of performance under the contract.

The Company recognizes milestone payments as revenue upon achievement of the milestone only if (1) the milestone payments are nonrefundable; (2) substantive effort is involved in achieving the milestone; and (3) the amount of the milestone is reasonable in relation to the effort expended or the risk associated with achievement of the milestone. If any of these conditions are not met, the Company defers the milestone payments and recognizes them as revenue over the estimated period of performance under the contract as the Company completes its performance obligations. In December 2004, the Company recognized revenue related to the receipt of a $2.0 million technology milestone payment from Merck under the Company's September 2003 collaboration agreement for the development of Systemic RNAi™ therapeutics (the "Technology Milestone").

Merck

The Company recognizes revenues from reimbursable research and development activities at the time these activities are performed under the terms of the related agreement, when the collaborator is obligated to pay and when no future performance obligations exist. In revenue arrangements where both parties reimburse each other for research costs, such as the Company's June 2004 collaboration agreement with Merck for the co-development of RNAi therapeutics for the treatment of ocular diseases, in which both parties reimburse each other for 50% of the costs incurred, as set forth in the agreement, the Company follows EITF Issue No. 01-9, *"Accounting for Consideration Given by a Vendor to a Customer (Including a Reseller of the Vendor's Products)"* ("EITF 01-9") in determining the proper accounting for these costs. In accordance with EITF 01-9, revenue recognized by the Company for costs reimbursed by the Company's customer are reduced by amounts reimbursable to the other party during the same accounting period unless the Company receives a separable and identifiable benefit in exchange for the payments made to the other party under the arrangement and the Company can reasonably estimate the fair value of the benefit received.

The Company has recorded revenues under our collaboration agreement with Merck for the co-development of RNAi therapeutics for the treatment of ocular diseases equal to $2.5 million in 2005 and $1.8 million in 2004, which represents amounts that the Company has earned for costs incurred under this agreement. As the above conditions do not exist with regard to this agreement, the Company has recorded reductions to revenues of $0.3 million in 2005 and 2004, which represent amounts owed to Merck for reimbursement of 50% of the costs incurred by Merck under the agreement.

Novartis

In consideration for rights granted to Novartis under the collaboration and license agreement, Novartis made an up-front payment of $10.0 million to the Company in October 2005, to partly reimburse prior costs incurred by the Company to develop *in vivo* RNAi technology. In addition, the collaboration and license agreement includes terms under which Novartis provides the Company with research funding and milestone payments as well as royalties on annual net sales of products resulting from the collaboration and license agreement. The Company has recorded as deferred revenue the non-refundable $10.0 million up-front payment and the $6.4 million premium received that represents the difference between the purchase price and the closing price of the common stock of the Company on the date of the stock purchase from Novartis. In addition to these payments, research funding and certain milestone payments will be amortized into revenue using the proportional performance method over the estimated duration of the Novartis agreement or ten years. Under this model, the Company will estimate the level of effort to be expended over the term of the agreement and recognize revenue based on the lesser of the amount

calculated based on proportional performance of total expected revenue or the amount of non-refundable payments earned.

The Company believes the estimated term of the Novartis agreement includes the three-year term of the agreement, two one-year extensions at the election of Novartis and limited support as part of a technology transfer until the fifth anniversary of the termination of the agreement. Therefore, an expected term of ten years is used in the proportional performance model. The Company will evaluate the expected term when new information is known that could affect the Company's estimate. In the event the Company's period of performance is different than estimated, revenue recognition will be adjusted on a prospective basis. The Company recognized approximately $0.7 million in revenues during 2005 this agreement.

Income Taxes

The Company uses the asset and liability method of accounting for income taxes. Under the liability method, deferred tax assets and liabilities reflect the impact of temporary differences between amounts of assets and liabilities for financial reporting purposes and such amounts as measured under enacted tax laws. A valuation allowance is required to offset any net deferred tax assets if, based upon the available evidence, it is more likely than not that some or all of the deferred tax asset will not be realized.

Research and Development Costs

Research and development costs are expensed as incurred. Included in research and development costs are wages, benefits and other operating costs such as legal expenses to secure and defend patents (which are expensed as incurred), facilities, supplies and overhead directly related to the Company's research and development department as well as costs to acquire technology licenses.

During the years ended December 31, 2005, 2004 and 2003, the Company included approximately $0.3 million, $1.3 million and $1.4 million of legal patent costs in research and development costs and expenses.

The Company has entered into several license agreements for rights to utilize certain technologies. The terms of the licenses may provide for up-front payments, annual maintenance payments, milestone payments based upon certain specified events being achieved and royalties on product sales. Costs to acquire and maintain licensed technology that has not reached technological feasibility and does not have alternative future use are charged to research and development expense as incurred. During the years ended December 31, 2005, 2004 and 2003, the Company charged to research and development expense $6.1 million, $5.8 million and $1.7 million, respectively, of costs associated with license fees (Note 12).

Accounting for Stock-Based Compensation

Employee stock awards granted under the Company's compensation plans are accounted for in accordance with Accounting Principles Board ("APB") Opinion No. 25, *"Accounting for Stock Issued to Employees"* ("APB 25"), and related interpretations. The Company has not adopted the fair value method of accounting for stock-based awards. All stock-based awards granted to non-employees are accounted for at their fair value in accordance with Financial Accounting Standards Board ("FASB") Statement of Financial Accounting Standards ("SFAS") No. 123 ("SFAS 123"), as amended, and Emerging Issues Task Force ("EITF") Issue No. 96-18, *"Accounting for Equity Instruments that are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling, Goods or Services"* ("EITF 96-18"), under which compensation expense is generally recognized over the vesting period of the award.

Under the intrinsic value method, compensation associated with stock-based awards to employees is determined as the difference, if any, between the current fair value of the underlying common stock on the date compensation is measured and the price an employee must pay to exercise the award. The measurement date for employee awards is generally the grant date. Under the fair-value method, compensation associated with stock-

based awards to non-employees is determined based on the estimated fair value of the award itself, measured using an established option pricing model. The measurement date for non-employee awards is generally the date performance of services is complete.

The Company provides the disclosure requirements of SFAS No. 148, *"Accounting for Stock Based Compensation — Transition and Disclosure, an amendment of FASB Statement No. 123"* ("SFAS 148"). If compensation expense for the Company's stock-based compensation plan had been determined based on the fair value at the grant dates as calculated in accordance with SFAS No. 123, the Company's net loss attributable to common stockholders and net loss per common share would approximate the pro forma amounts below, in thousands, except per share amounts:

	2005	2004	2003
Net loss attributable to common stockholders			
Net loss, as reported	$(42,914)	$(35,367)	$(27,939)
Add employee stock-based compensation expense included in reported net loss	2,484	3,137	667
Deduct employee stock-based compensation expense determined under fair value method	(6,285)	(3,448)	(697)
Net loss — pro forma	$(46,715)	$(35,678)	$(27,969)
Net loss per common share (basic and diluted)			
As reported	$ (1.96)	$ (2.98)	$ (29.64)
Pro forma	$ (2.13)	$ (3.00)	$ (29.67)

For the year ended December 31, 2003, the Company estimated the fair value of its stock option grants by applying a present value approach which does not consider expected volatility of the underlying stock ("minimum value method") since the Company's common stock was not publicly traded. For 2005 and 2004, the Company estimated the fair value of its stock option grants using the Black-Scholes option pricing model. Assumptions used in these fair values are as follows:

	2005	2004	2003
Risk-free interest rate	3.97%	3.60%	3.19%
Expected dividend yield	—	—	—
Expected option term	5 years	5 years	5 years
Volatility	68%	88%	—

Redeemable Convertible Preferred Stock

Redeemable convertible preferred stock was treated as if it was mandatorily redeemable (formerly classified in the mezzanine section of the balance sheet) if it may have been redeemed by the holder based on facts and circumstances not in the Company's control. If there was a specified redemption date, the carrying value was accreted to its redemption value over the term. These adjustments were affected through charges first against retained earnings, then against additional paid-in capital until it is reduced to zero and then to accumulated deficit.

Foreign Currency

The Company's foreign subsidiary, Alnylam Europe AG (a German based company), has designated its local currency, the Euro, as its functional currency. Financial statements of this foreign subsidiary are translated to United States dollars for consolidation purposes using current rates of exchange for assets and liabilities; equity is translated using historical exchange rates; and revenue and expense amounts are translated using the average exchange rate for the period. Net unrealized gains and losses resulting from foreign currency translation are

included in other comprehensive income (loss) which is a separate component of stockholders' equity. The Company also records a charge or a credit to stockholders' equity for exchange gains or losses on intercompany balances that are of a long-term nature. Net realized gains and losses from foreign currency transactions are included in the consolidated statement of operations. The Company recognized a gain of $119,000 during 2005, a loss of $231,000 during 2004 and a gain of $51,000 during 2003 from foreign currency transactions.

Comprehensive Loss

Comprehensive loss is comprised of net loss and certain changes in stockholders' equity that are excluded from net loss. The Company includes foreign currency translation adjustments in other comprehensive loss for Alnylam Europe AG as the functional currency is not the United States dollar.

Net Loss Per Common Share

The Company accounts for and discloses net loss per common share in accordance with SFAS No. 128 *"Earnings per Share"*. Basic net loss per common share is computed by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding. Diluted net loss per common share is computed by dividing net loss attributable to common stockholders by the weighted average number of common shares and dilutive potential common share equivalents then outstanding. Potential common shares consist of shares issuable upon the exercise of stock options and warrants (using the treasury stock method), unvested restricted stock awards and the weighted average conversion of the preferred stock into shares of common stock (using the if-converted method) for periods prior to the Company's initial public offering, which was completed in June 2004. Because the inclusion of potential common stock would be anti-dilutive for all periods presented, diluted net loss per share is the same as basic net loss per share.

The following table sets forth the potential common stock excluded from the calculation of net loss per share because their inclusion would be anti-dilutive:

	December 31,		
	2005	2004	2003
Options to purchase common stock	3,907,127	2,851,967	1,693,530
Warrants to purchase common stock	52,630	52,630	13,157
Convertible preferred stock	—	—	11,087,696
Unvested restricted common stock	55,063	331,567	645,385
Options that were exercised before vesting	72,796	118,563	15,789
	4,087,616	3,354,727	13,455,557

Segment Information

The Company has two operating segments, U.S. and Germany, which management aggregates into one reporting unit in determining how to allocate resources and assess financial performance. For this reason, the Company has determined that it is principally engaged in one industry segment.

The following table presents total long-lived tangible assets by geographic area as of December 31, 2005 and 2004, in thousands:

	December 31, 2005	December 31, 2004
Long-lived tangible assets:		
United States	$ 8,207	$ 8,919
Germany	2,373	2,775
Total long-lived tangible assets	$10,580	$11,694

Recent Accounting Pronouncements

In December 2004, the FASB issued SFAS No. 123R, *"Share-Based Payment"* ("SFAS 123R"), which revises SFAS No. 123, *"Accounting for Stock-based Compensation"* and requires companies to expense the fair value of employee stock options and other forms of stock-based compensation. Under SFAS 123R, the most significant change in practice would be treating the fair value of stock based payment awards that are within its scope as compensation expense in the income statement beginning on the date that a company grants the awards to employees. In April 2005, the SEC delayed the effective date of SFAS 123R to financial statements issued for the first annual period beginning after June 15, 2005. As a result, the Company will adopt and comply with the requirements of SFAS 123R in the three months ending March 31, 2006. The Company is currently assessing the impact that the adoption of this standard will have on its financial position and results of operations and the method by which the Company will implement this standard, however, the Company expects stock compensation expense to materially increase as a result of the adoption of this standard.

In May 2005, the FASB issued SFAS No. 154, *"Accounting Changes and Error Corrections"* ("SFAS 154"). SFAS 154 is a replacement of APB No. 20 and FASB Statement No. 3. SFAS 154 provides guidance on the accounting for and reporting of accounting changes and error corrections. It establishes retrospective application as the required method for reporting a change in accounting principle. SFAS 154 provides guidance for determining whether retrospective application of a change in accounting principle is impracticable and for reporting a change when retrospective application is impracticable. The reporting of a correction of an error by restating previously issued financial statements is also addressed by SFAS 154. SFAS 154 is effective for accounting changes and corrections of errors made in fiscal years beginning after December 15, 2005. The Company does not expect the adoption of SFAS 154 will have a material impact on the Company's financial position or results of operations.

3. ACQUISITION OF RIBOPHARMA AG

On July 31, 2003, Alnylam acquired all the outstanding voting shares of Ribopharma AG, a German-based company now called Alnylam Europe AG. The results of operations of Ribopharma AG are included in the operating results of the Company from the date of acquisition (July 31, 2003). At the date of acquisition, Ribopharma was a development stage enterprise performing research and development associated with a new pharmaceutical active agent category siRNA, which it continues to do as a wholly-owned subsidiary. Alnylam purchased Ribopharma for access to its in-process research and development programs and its core technology. In addition, the acquisition of Ribopharma enabled Alnylam to satisfy the conditions in the technology license agreement with Garching Innovation GmbH ("Garching") (Note 12) to establish a German-based company with comparable operational force and resources. Satisfaction of this condition enabled Alnylam to convert its co-exclusive rights under the Garching license to exclusive rights.

The consideration consisted of $1.5 million in cash and 815,376 shares of common stock. Based on a valuation performed of Ribopharma AG and the intangible assets acquired, the purchase price was estimated at $3.9 million and comprised of the following, in thousands:

Cash paid	$1,500
Fair value of common stock issued	1,947
Acquisition costs	419
	$3,866

The fair value of the tangible and intangible assets acquired and liabilities assumed were recorded as follows, in thousands:

Cash	$ 1,798
Other current assets	41
Fixed assets	1,733
Intangible assets	8,684
Accounts payable and accrued expenses assumed	(1,300)
Notes payable assumed	(7,090)
	$ 3,866

The appraised value of intangible assets acquired was below the total fair value of intangible assets acquired and would generally result in the recognition of goodwill. However, since Ribopharma AG was a development stage company and not considered a "business" as defined by the applicable accounting rules at the date of acquisition, this residual value was allocated proportionately to the long-lived assets acquired as follows, in thousands:

	Fair Value
Purchased in-process research and development	$ 4,609
Core technology	3,638
Workforce	437
Fixed assets	1,733
	$10,417

The fair market value of the intangible assets acquired was based on a valuation and determined using an income approach. The core technology was valued using a relief from royalty methodology, the purchased in-process research and development was valued based on a discounted cash flow analysis and the workforce was valued using the avoided cost method.

Purchased in-process technology was written off immediately upon the consummation of the acquisition and is included as a separate line in the Company's statement of operations. Core technology and workforce are being amortized over their estimated useful lives of ten years and four years, respectively. The step up in the fixed assets is being amortized over four years, the remaining estimated useful life of these assets.

Intangible assets at December 31, 2005 and 2004 are as follows, in thousands:

	December 31, 2005	December 31, 2004
Core Technology	$ 3,197	$3,638
Workforce	437	437
	3,634	4,075
Less — accumulated amortization:		
Core Technology	(879)	(515)
Workforce	(264)	(155)
Total accumulated amortization	(1,143)	(670)
	$ 2,491	$3,405

During the years ended December 31, 2005, 2004 and 2003, the Company recorded $473,000, $473,000 and $197,000, respectively, of amortization expense related to the core technology and workforce intangibles, of which the entire amount is included in research and development expenses. During the years ended December 31, 2005, 2004 and 2003, the Company recorded $295,000, $295,000 and $123,000, respectively, of additional depreciation related to the increase in the recorded fair value of the fixed assets, of which $265,000, $265,000 and $111,000 is included in research and development expenses in 2005, 2004 and 2003, respectively, and $30,000, $30,000 and $12,000 is included in general and administrative expense in 2005, 2004 and 2003, respectively. The Company expects annual amortization expense related to the core technology intangible asset to be $306,000 through 2012 and $178,000 in 2013. The Company also expects annual amortization expense related to the workforce intangible asset to be $109,000 through 2006 and $64,000 in 2007. During 2005, the Company reduced its intangible assets by $441,000 related to the utilization of pre-acquisition deferred tax assets associated with net operating losses.

Purchased In-Process Research and Development

In connection with the Company's acquisition of Ribopharma AG, the Company acquired two Systemic RNAi programs related to the development of drugs targeting cancers such as malignant melanoma and pancreatic carcinoma. The Company expensed $4.6 million of purchased in-process research and development associated with these programs. Management's plans contemplate that the Company will conduct the first phase of clinical trials and then out-license the programs to a partner. Upon out-licensing, the partner is expected to bear all development costs and control clinical development. The Company expects to earn payments upon the attainment of clinical milestones by its partner and royalties on product sales. Since the partner will control the clinical development, the Company will be unable to influence the timing of the achievement of the milestones, if at all, or the estimated year of the product launch, if at all. The Company's valuation assumed a development period of approximately 10 years, with milestones being earned during that period, which management believes is a typical horizon to bring a therapeutic drug to market. Actual results will differ from these estimates due to the uncertainties surrounding drug development.

Management assumes responsibility for determining the in-process research and development valuation. The fair value assigned to purchase in-process research and development was estimated by discounting, to present value, the probability-adjusted net cash flows expected to result once the technology has reached technological feasibility. A discount rate of 32 percent was applied to estimate the present value of the cash flows and is consistent with the overall risks of developing these projects. As of December 31, 2005, the technological feasibility of the projects had not been reached and management believes the assumptions included in the valuation analysis continue to be valid. In the allocation of the purchase price, the concept of alternative future use was considered. The projects under development have no current alternative future uses for the underlying technology in the event the projects are unsuccessful.

4. PROPERTY AND EQUIPMENT

Property and equipment consist of the following at December 31, 2005 and 2004, in thousands:

	Useful Life	December 31, 2005	December 31, 2004
Laboratory equipment	5 years	$ 7,799	$ 6,652
Computer equipment and software	3 years	1,265	808
Furniture and fixtures	5 years	571	795
Leasehold improvements	*	6,010	5,902
Construction in progress	—	32	—
		15,677	14,157
Less: accumulated depreciation and amortization		(5,097)	(2,463)
		$10,580	$11,694

* shorter of asset life or lease term

Depreciation expense was $2.6 million, $2.0 million, and $0.6 million for the years ended December 31, 2005, 2004 and 2003 respectively.

5. ACCRUED EXPENSES

Accrued expenses consist of the following at December 31, 2005 and 2004, in thousands:

	December 31, 2005	December 31, 2004
License fee payable to Isis	$ —	$2,000
Other	3,899	685
	$3,899	$3,875

6. NOTES PAYABLE

Note Payable to a Bank

In December 2002, the Company entered into an agreement with Silicon Valley Bank to establish an equipment line of credit for $2.5 million. The Company drew down a total of $2.1 million on this line of credit during 2003, of which $239,000 was paid in 2003 and the remainder was repaid in March 2004 in connection with the Company's establishment of a new line of credit. Under the terms of the agreement with Silicon Valley Bank, borrowings bore interest at prime rate plus 0.25% as well as additional interest of 8.0% of the original principal payable upon the maturity of each equipment advance under this line of credit. In 2005 and 2004, the Company recorded interest expense of zero and $202,000, respectively, related to borrowings under this line of credit. Interest expense recorded in 2004 included $168,000 of interest penalties paid upon the early repayment of this line of credit. In March 2004, the Company paid off the remaining balance of the loan with Silicon Valley Bank, of $1.9 million, via an initial draw in the amount of the payoff balance, in conjunction with establishing an equipment line of credit.

Equipment Line of Credit

In March 2004, the Company entered into an agreement with Lighthouse Capital Partners V, L.P. ("Lighthouse") to establish an equipment line of credit for $10.0 million. In June 2005, the parties amended the agreement

to allow the Company the ability to draw down amounts under the line of credit through December 31, 2005 upon adherence to certain conditions. All borrowings under the line of credit are collateralized by the assets financed and the agreement contains certain provisions that restrict the Company's ability to dispose of or transfer these assets. The outstanding principal bears interest at a fixed rate of 9.25%, except for the drawdown made in December 2005, which bears interest at a fixed rate of 10.25%, maturing at various dates through December 2009. The Company was required to make interest only payments on all draw-downs made during the period from March 26, 2004 through June 30, 2005 at which point all draw-downs began to be repaid over 48 months. On the maturity of each equipment advance under the line of credit, the Company is required to pay, in addition to the paid principal and interest, an additional amount of 11.5% of the original principal. This amount is being accrued over the applicable borrowing period as additional interest expense.

In connection with the agreement, the Company issued to Lighthouse and an affiliate of Lighthouse warrants to purchase redeemable convertible preferred stock, which were converted into warrants to purchase 52,630 shares of the Company's common stock at an exercise price of $9.50 per share upon the closing of the Company's initial public offering in June 2004. The Company recorded the fair value of these warrants of $0.6 million as a deferred financing cost which is being amortized to interest expense over the repayment term of the first advance of 63 months. The fair value of the warrants was calculated using the Black-Scholes option pricing model with the following assumptions: 100% volatility, risk-free interest rate of 3.49%, no dividend yield, and a seven-year term.

As of December 31, 2005, future cash payments under the note payable to Lighthouse, including interest, are as follows, in thousands:

Year Ending December 31,	
2006	$2,462
2007	2,462
2008	2,463
2009	2,179
Total through 2009	9,566
Less: portion representing interest	2,171
Principal	7,395
Less: current portion	1,876
Long-term note payable	$5,519

Note Payable to Ribopharma AG Shareholder

Upon the acquisition of Ribopharma AG, Alnylam Pharmaceuticals, Inc. assumed a note payable and accrued interest of $4.8 million to a Ribopharma shareholder and an obligation to provide common shares based on prior terms of the note valued at $119,000, both of which were included in assumed liabilities upon the acquisition date. The note payable of $4.5 million and accrued interest of $0.3 million were exchanged for 1,917,857 shares of Series B preferred stock. Additionally, 49,496 shares of Alnylam Pharmaceuticals, Inc.'s common stock were issued to satisfy the obligation to provide shares. There were no amounts outstanding under this note payable as of December 31, 2005 or 2004.

7. COMMITMENTS AND CONTINGENCIES

Indemnifications

Licensor indemnification — In connection with a certain license agreement, the Company is required to indemnify the licensor for certain damages arising in connection with the intellectual property rights licensed under

the agreement. The Company believes that the probability of receiving a claim is remote and, as such, no amounts have been accrued related to this indemnification as of December 31, 2005 and 2004.

The Company is also a party to a number of agreements entered into in the ordinary course of business, which contain typical provisions, which obligate the Company to indemnify the other parties to such agreements upon the occurrence of certain events. Such indemnification obligations are usually in effect from the date of execution of the applicable agreement for a period equal to the applicable statute of limitations. The aggregate maximum potential future liability of the Company under such indemnification provisions is uncertain. Since its inception, the Company has not incurred any expenses as a result of such indemnification provisions. Accordingly, the Company has determined that the estimated aggregate fair value of its potential liabilities under such indemnification provisions is minimal and has not recorded any liability related to such indemnification provisions as of December 31, 2005 and 2004.

Technology License Commitments

The Company has licensed the rights to use certain technologies in its research process as well as in any products the Company may develop including these licensed technologies. In accordance with the related license agreements, the Company is required to make certain fixed annual payments to the licensor or a designee of the licensor over various agreement terms. Many of these agreement terms are consistent with the remaining lives of the underlying intellectual property that the Company has licensed. At December 31, 2005, the Company was committed to make the following fixed license payments under existing license agreements, in thousands:

Year Ending December 31,	
2006	$ 335
2007	335
2008	335
2009	335
2010	335
Thereafter	3,660
Total	$5,335

Operating Leases

The Company leases office and laboratory space in Cambridge, Massachusetts and Kulmbach, Germany (beginning on July 31, 2003, the date of acquisition of Ribopharma AG), under non-cancelable operating lease agreements. Total rent expense, including operating expenses, under these operating leases was $1.9 million, $2.2 million, and $1.0 million, for the years ended December 31, 2005, 2004 and 2003, respectively.

In September 2003, the Company entered into an operating lease to rent 33,453 square feet of laboratory and office space in Cambridge, Massachusetts through September 2011. Rental payments began in April 2004. Under the original terms of the lease agreement, the Company began paying rent on an additional 10,605 square feet in this same facility in September 2005. In March 2006, the Company amended its lease agreement and will begin paying rent on an additional 17,823 square feet in this same facility on July 1, 2006, bringing the total square feet leased in Cambridge to 61,881 square feet. The Company has the option to extend the lease for two successive five-year extensions.

Pursuant to the terms of the lease agreement, the Company secured a $2.3 million letter of credit as security for its leased facility. The underlying cash securing this letter of credit has been classified as long-term restricted cash in the accompanying consolidated balance sheets.

The Company also leases 13,585 square feet of laboratory and office space in Kulmbach, Germany through June 2008 under a non-cancelable operating lease. The Company began paying rent on an additional 1,439 square feet in the same facility in March 2005. The Company has the option to extend its lease of this facility for two successive three-year extensions.

Future minimum lease payments under these non-cancelable leases are approximately as follows, thousands:

Year Ending December 31,	
2006	$ 2,231
2007	2,390
2008	2,397
2009	2,218
2010	2,218
Thereafter	1,663
Total	$13,117

Related Party Notes Receivable

In connection with the acquisition of Ribopharma AG, the Company agreed to provide two shareholders of Ribopharma AG who received cash and common stock in the acquisition with non-recourse loans to cover any tax contingencies the shareholders may incur as a result of the acquisition. These loans bear interest at four percent per annum and are payable upon certain liquidity events. In addition to the loan commitment, the Company entered into an indemnity agreement whereby the Company has indemnified these shareholders for any taxes payable as a result of making the loan to the Ribopharma shareholders up to a maximum of approximately $179,000 for each shareholder. With respect to the indemnity, the Company issued a letter of credit in 2003 to the two shareholders amounting to $354,000 related to the potential indemnity that the Company has with the two shareholders. The required amount of the letter of credit is collateralized by restricted funds maintained by the Company at the bank issuing the letter of credit. As a result, the Company classified this amount as restricted cash in its consolidated balance sheet as of December 31, 2003. In June 2004, loans totaling approximately $304,000 were provided to these shareholders and each shareholder subsequently released the Company from its indemnity obligation. As a result, the Company cancelled its letter of credit and removed this restriction of its cash. During December 2005, one of the notes for $135,000 was paid in full. At December 31, 2005, the remaining amount under the note receivable was $146,000, including accrued interest. The remaining related party note receivable was paid in full in February 2006.

In connection with the employment agreements of the same two Ribopharma AG employees, the Company has committed to paying a one-time payment to each employee of $250,000 upon the issuance of a specific patent in the United States of America. This contingent payment will be paid and expensed upon the issuance of the patent.

Legal Proceedings

The Company may periodically become subject to legal proceedings and claims arising in connection with on-going business activities, including being subject to claims or disputes related to patents that have been issued or are pending in the field of research the Company is focused on. The Company does not believe that there were any material claims against the Company as of December 31, 2005.

8. STOCKHOLDERS' EQUITY

Preferred Stock

Prior to the Company's initial public offering in June 2004, the Company's primary source of funding was from sales of preferred stock, both convertible and redeemable convertible. During 2004, 2003 and 2002, the Company

sold 1,666,667, 12,906,670 and 8,160,010 shares of preferred stock, respectively, which resulted in net proceeds of $10.0 million, $34.5 million and $17.3 million, respectively. During the years ended December 31, 2005, 2004 and 2003, the Company recorded accretion of preferred stock of zero, $2.7 million and $2.9 million, respectively. In connection with the Company's initial public offering in June 2004, and in accordance with the preferred stock agreements, all outstanding shares of preferred stock converted into 11,964,908 of the Company's common stock. At December 31, 2005 and 2004, there were no shares of preferred stock outstanding.

The Company has authorized up to 5,000,000 shares of preferred stock, $0.01 par value per share, for issuance. The preferred stock will have such rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, as shall be determined by the board of directors upon its issuance.

Stockholder Rights Agreement

On July 13, 2005, the Board of Directors of the Company declared a dividend of one right (collectively, the "Rights") to buy one one-thousandth of a share of newly designated Series A Junior Participating Preferred Stock ("Series A Junior Preferred Stock") for each outstanding share of the Company's common stock to stockholders of record at the close of business on July 26, 2005. Initially, the Rights are not exercisable and will be attached to all certificates representing outstanding shares of common stock, and no separate Rights Certificates will be distributed. The Rights will expire at the close of business on July 13, 2015 unless earlier redeemed or exchanged. Until a right is exercised, the holder thereof, as such, will have no rights as a stockholder of the Company, including the right to vote or to receive dividends. The rights are not immediately exercisable. Subject to the terms and conditions of the Rights Agreement entered into by the Company with Computershare (formerly EquiServe Trust Company, N.A.), as Rights Agent (the "Rights Agreement"), the Rights will become exercisable upon the earlier of (1) 10 business days following the later of (a) the first date of a public announcement that a person or group (an "Acquiring Person") acquires, or obtained the right to acquire, beneficial ownership of 20 percent or more of the outstanding shares of common stock of the Company or (b) the first date on which an executive officer of the Company has actual knowledge that an Acquiring Person has become such or (2) 10 business days following the commencement of a tender offer or exchange offer that would result in a person or group beneficially owning more than 20 percent of the outstanding shares of common stock of the Company. Each right entitles the holder to purchase one one-thousandth of a share of Series A Junior Preferred Stock at an initial purchase price of $80.00 in cash, subject to adjustment. In the event that any person or group becomes an Acquiring Person, unless the event causing the 20% threshold to be crossed is a Permitted Offer (as defined in the Rights Agreement), each Right not owned by the Acquiring Person will entitle its holder to receive, upon exercise, that number of shares of common stock of the Company (or in certain circumstances, cash, property or other securities of the Company) which equals the exercise price of the Right divided by 50% of the current market price (as defined in the Rights Agreement) per share of such common stock at the date of the occurrence of the event. In the event that, at any time after any person or group becomes an Acquiring Person, (i) the Company is consolidated with, or merged with and into, another entity and the Company is not the surviving entity of such consolidation or merger (other than a consolidation or merger which follows a Permitted Offer) or if the Company is the surviving entity, but shares of its outstanding common stock are changed or exchanged for stock or securities (of any other person) or cash or any other property, or (ii) more than 50% of the Company's assets or earning power is sold or transferred, each holder of a Right (except Rights which previously have been voided as set forth in the Rights Agreement) shall thereafter have the right to receive, upon exercise, that number of shares of common stock of the acquiring company which equals the exercise price of the Right divided by 50% of the current market price of such common stock at the date of the occurrence of the event.

Founders' Shares

In June 2002, the Company sold 1,294,716 shares of common stock to the Company's founders, including certain non-employees, in exchange for $0.0001 per share, which represented the fair market value of the common stock on the date of sale, as determined by management and approved by the board of directors. The founders'

common stock is subject to restricted stock agreements, which include various restrictions, including the right of the Company to repurchase declining percentages of the shares at the original issuance price during the four-year period following issuance if the employee or non-employee ceases to provide services to the Company for any reason. In July 2002, the Company sold 47,368 shares of common stock to a consultant for $0.19 per share, which represented the fair market value of the common stock on the date of sale, as determined by management. This common stock is subject to a restricted stock agreement, which includes various restrictions, including the right of the Company to repurchase declining percentages of the shares at the original issuance price during the four-year period following issuance if the consultant ceases to perform services.

In connection with the restricted stock awards issued to non-employees, the Company has recorded cumulative deferred compensation of $3.7 million, which represents the cumulative fair value of the restricted stock awards measured in accordance with SFAS No. 123 and EITF 96-18. Shares remaining unvested or subject to forfeiture for non-employees still providing services are subject to a mark-to-market adjustment during each reporting period prior to vesting in full. The deferred compensation will be recorded as an expense over the vesting period of the underlying restricted stock using the method prescribed by FIN No. 28, *Accounting for Stock Appreciation Rights and Other Variable Stock Options or Award Plans*, ("FIN 28"). The Company recorded $1.0 million, $0.2 million, and $2.2 million of compensation expense during the years ended December 31, 2005, 2004 and 2003, respectively, related to the amortization of the deferred compensation. The deferred compensation balance at December 31, 2005, 2004, and 2003, respectively, related to these awards was $0.1 million, $0.4 million and $1.2 million. Since the fair market value of the common stock issued to non-employees is subject to change in the future, the compensation expense recognized during the year ended December 31, 2005, and prior years may not be indicative of future compensation charges.

Reverse Stock Split

On May 7, 2004, the Company effected a reverse 1-for-1.9 split of all outstanding shares of common stock. All common share and per share data have been retroactively restated to reflect this event.

Initial Public Offering

In June 2004, the Company completed the initial public offering of its common stock. The initial public offering consisted of the sale of 5,000,000 shares of common stock at a price of $6.00 per share. As part of the offering, the Company granted to the underwriters an option to purchase an additional 750,000 shares within 30 days of the initial public offering to cover over-allotments. This option was exercised in full in June 2004. Net proceeds from the initial public offering after deducting underwriters' discounts and expenses were $29.9 million. Upon the closing of the initial public offering, the authorized number of shares of the Company's common stock increased to 125,000,000. In addition, upon the closing of the Company's initial public offering, the Company adopted certain stock incentive plans (Note 9).

Public Offering of Common Stock

On January 31, 2006, the Company completed a public offering of its common stock. The public offering consisted of the sale and issuance of 5,115,961 shares of the Company's common stock. The Company granted the underwriters an option to purchase up to an additional 767,394 shares of common stock within 30 days after the offering to cover over-allotments, which option was not exercised. The price to the public was $13.00 per share, and proceeds to the Company from the offering, net of expenses, were approximately $62.3 million. The shares of common stock were registered pursuant to registration statements filed with Securities and Exchange Commission in 2006 and 2005.

9. STOCK INCENTIVE PLANS

Stock Option Plans

Prior to the Company's initial public offering in June 2004, the Company had adopted stock incentive plans in 2002 and 2003. In June 2002, the Company adopted the 2002 Stock Incentive Plan (the "2002 Stock Plan"), which was terminated in November 2002, and was replaced with the Alnylam U.S., Inc. 2002 Employee, Director and Consultant Stock Plan (the "2002 Plan"). All options previously granted under the 2002 Stock Plan were canceled and new options for the same number of shares, vesting provisions and exercise price were granted under the 2002 Plan. In September 2003, the Company adopted the Alnylam Pharmaceuticals, Inc. 2003 Employee, Director and Consultant Stock Plan (the "2003 Plan"). Subsequent to the closing of the Company's initial public offering, no further stock options or other equity awards have been granted, or may be granted in the future, under the 2002 Plan or the 2003 Plan.

As of December 31, 2005, the Company's 2004 Stock Incentive Plan (the "2004 Plan") provides for the granting of stock options to purchase 5,072,702 shares of common stock. The 2004 Plan provides for an annual increase in the number of shares available for issuance under the plan equal to the lesser of 2,631,578 shares of common stock, 5% of the Company's outstanding shares or an amount determined by the board of directors. In addition, the 2004 Plan includes a non-employee director stock option program under which each eligible non-employee director will be entitled to a grant of options to purchase 25,000 shares of common stock upon his or her initial appointment to the board of directors and a subsequent annual grant of an option to purchase 10,000 shares of common stock based on continued service. The chairman of the audit committee will receive an additional annual grant of an option to purchase 10,000 shares of common stock based on continued service.

As of December 31, 2005, an aggregate of 4,578,704 shares of common stock were reserved for issuance under the 2004 Plan, including outstanding options to purchase 3,907,127 shares of common stock and 671,577 shares were available for future grant.

The plans provide for the granting of incentive stock options ("ISOs") and nonqualified stock options. Stock options may be granted to the Company's employees, officers, directors, consultants and advisors, as defined. ISOs may be granted at no less than fair market value on the date of grant, as determined by the Company's Board of Directors (no less than 110 percent of fair market value on the date of grant for 10 percent or greater stockholders), subject to certain limitations. Each option shall be exercisable at such times and subject to such terms as determined by the Board of Directors and expires within ten years of issuance.

Options granted generally vest at a rate of 25 percent on the first anniversary of the grant date and 6.25 percent of the shares each successive three-month period until fully vested. In January 2004, the Company granted an option to the chief executive officer to purchase 105,263 shares of common stock at an exercise price of $0.95 per share that vested in full upon the Company's initial public offering in June 2004. In December 2004, the Company granted an option to the chief executive officer to purchase up to 250,000 shares of common stock at an exercise price of $7.47 per share that vested in full upon the upon the effective date of the Novartis Collaboration and License Agreement (as defined below).

The following table summarizes the activity of the Company's stock option plans:

	Number of Options Available for Future Grant	Number of Options	Weighted Average Exercise Price
Outstanding, December 31, 2002	681,263	81,894	$ 0.48
Granted		1,656,187	0.53
Exercised		(44,526)	0.48
Cancelled		—	—
Outstanding, December 31, 2003	498,761	1,693,555	0.53
Granted		1,590,474	5.39
Exercised		(249,724)	0.74
Cancelled		(182,338)	0.56
Outstanding, December 31, 2004	884,045	2,851,967	2.91
Granted		1,265,463	18.10
Exercised		(189,750)	1.58
Cancelled		(20,553)	10.74
Outstanding, December 31, 2005	671,577	3,907,127	$ 5.73
Exercisable at December 31, 2003		192,711	$ 0.48
Exercisable at December 31, 2004		724,097	$ 0.57
Exercisable at December 31, 2005		1,550,510	$ 2.54

All options granted during the year ended December 31, 2003 had an exercise price that was less than the fair value of common stock on the date of grant. The weighted average fair value of these options was $2.38. During 2004, the Company granted options to purchase 544,984 shares of common stock with exercise prices that were less than the fair value of the Company's common stock on the date of grant. The weighted average fair value of these options was $4.89. In addition, during 2004, the Company granted options to purchase 1,045,485 shares of common stock with exercise prices that were equal to the market price of the Company's common stock on the date of grant. The weighted average fair value of these options was $5.17. During 2005, the Company granted options to purchase 1,265,463 shares of common stock with exercise prices that were equal to the market price of the Company's common stock on the date of grant.

The following table summarizes information about stock options outstanding and exercisable at December 31, 2005:

	Options Outstanding			Options Exercisable	
Exercise Price Range	Number of Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life (in years)	Number of Options	Weighted Average Exercise Price
$ 0.48	1,013,817	$ 0.48	7.35	781,111	$0.47
$ 0.95	602,390	$ 0.95	8.04	305,416	$0.95
$ 5.23 - $ 6.78	761,916	$ 6.61	8.90	200,161	$6.58
$ 6.86 - $12.66	715,621	$ 7.86	9.29	263,822	$7.45
$12.89 - $13.82	813,383	$13.12	9.94	—	
	3,907,127			1,550,510	

During the years ended December 31, 2005, 2004 and 2003, in connection with the grant of common stock options to employees, the Company recorded deferred stock compensation of approximately zero, $3.7 million and $3.3 million, respectively, representing the difference between the exercise price and the fair market value of the Company's common stock on the date the stock options were granted. During the years ended December 31, 2005, 2004 and 2003, the Company recorded amortization of deferred stock compensation of $1.8 million, $3.1 million and $0.7 million, respectively, and $1.1 million remains unamortized at December 31, 2005. The Company will be recognizing the fixed deferred stock compensation over the remaining vesting period of the options, subject to forfeitures should the employees terminate, in accordance with the method prescribed by FIN 28. The anticipated future amortization of deferred stock compensation related to employee option grants as of December 31, 2005 is as follows, in thousands:

Year Ending December 31,	
2006	$ 788
2007	317
2008	17
	$1,122

In connection with stock options granted to non-employees for services during the years ended December 31, 2005, 2004 and 2003, the Company has recorded aggregate deferred compensation of $2.5 million, which represents the fair value of non-employee grants. The deferred compensation will be recorded as an expense over the vesting period of the underlying stock options using the method prescribed by FIN 28. At the end of each financial reporting period prior to vesting, the value of these options (as calculated using the Black-Scholes option pricing model) will be re-measured using the then current fair value of the Company's common stock. At that point, deferred compensation and the non-cash compensation recognized during that period will be adjusted accordingly. Since the fair market value of the common stock options granted to non-employees is subject to change in the future, the amount of future compensation expense recognized will be adjusted until the stock options are fully vested. Stock-based compensation expense related to these non-employee options for the years ended December 31, 2005, 2004 and 2003 was $1.2 million, $0.7 million and $0.5 million, respectively.

Employee Stock Purchase Plan

In 2004, the Company adopted the 2004 Employee Stock Purchase Plan (the "2004 Purchase Plan") with 315,789 shares authorized for issuance. Under the 2004 Purchase Plan, the Company makes one offering each year, at the end of which employees may purchase shares of common stock through payroll deductions made over the term of the offering. The per-share purchase price at the end of the offering is equal to the lesser of 85% of the closing price of the common stock at the beginning or end of the offering period. The annual offering period begins on the 1st day of November each year and ends on the 31st day of October each year. The Company issued 51,792 shares under the 2004 Purchase Plan during 2005.

10. INCOME TAXES

Deferred income taxes reflect the tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting and income tax purposes. A valuation allowance is established when uncertainty exists as to whether all or a portion of the net deferred tax assets will be realized. Components of the net deferred tax asset as of December 31, 2005 and 2004, are approximately as follows, in thousands:

	2005	2004
Deferred Tax Assets:		
Net operating loss carryforwards	$ 10,248	$ 5,863
Research and development credits	2,153	1,000
Capitalized research and development and start-up costs	15,931	12,962
Deferred revenue	8,390	2,047
Other	2,372	634
Total deferred tax assets	39,094	22,506
Deferred Tax Liabilities:		
Intangible assets	(1,104)	(1,371)
Deferred tax asset valuation allowance	(37,690)	(21,135)
Net deferred tax asset	$ 300	$ —

The Company's effective income tax rate differs from the statutory federal income tax rate as follows for the years ended December 31, 2005, 2004 and 2003:

	2005	2004	2003
At U.S. federal statutory rate	34.0%	34.0%	34.0%
State taxes, net of federal effect	5.6	5.4	5.0
Permanent items	(3.4)	(3.8)	(2.2)
Purchased in-process research and development	—	(0.1)	(6.0)
Federal research credits	2.5	1.9	0.6
Valuation allowance	(38.4)	(37.4)	(31.4)
Effective income tax rate	0.3%	0.0%	0.0%

As required by SFAS No. 109, management of the Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Management has concluded, in accordance with the applicable accounting standards, that it is more likely than not that the Company may not realize the benefit of its deferred tax assets, except for approximately $0.3 million related to its subsidiary, Alnylam Europe AG. Accordingly, the deferred tax assets have been fully reserved except for $0.3 million related to Alnylam Europe AG. Management reevaluates the positive and negative evidence on an annual basis.

At December 31, 2005, the Company had federal and state net operating loss carryforwards of approximately $21.4 million and $20.3 million available, respectively, to reduce future taxable income and which will expire at various dates beginning in 2007 through 2025. At December 31, 2005, federal and state research and development and other credit carryforwards were approximately $1.4 million and $1.2 million, respectively, available to reduce future tax liabilities, and, which expire at various dates beginning in 2017 through 2025. Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in connection with the Company's planned initial public offering, may limit the amount of net operating loss and tax credit carryforwards that can be utilized to offset future taxable income or tax liability. The amount of the limitation is determined in accordance with Section 382 of the Internal Revenue Code.

11. 401(K) SAVINGS PLAN

The Company sponsors a savings plan for its employees, who meet certain eligibility requirements, which is designed to be a qualified plan under section 401(k) of the Internal Revenue Code (the "401(k) Plan"). The 401(k) Plan allows participants to defer up to 15 percent of their annual compensation and with proper notice up to 100 percent of their compensation in the final month of the plan year on a pretax basis and subject to Internal Revenue Code limits. The plan covers substantially all of the employees who meet minimum age and service requirements. The Company may make matching contributions to the 401(k) Plan in amounts determined by the Company's Board of Directors. The Company did not contribute to the 401(k) plan during the years ended December 31, 2005, December 31, 2004 or December 31, 2003.

12. SIGNIFICANT AGREEMENTS

Novartis Broad Alliance

Beginning in September 2005, the Company entered into a series of transactions with Novartis. In September 2005, the Company and Novartis executed a stock purchase agreement (the "Stock Purchase Agreement") and an investor rights agreement (the "Investor Rights Agreement"). In October 2005, in connection with the closing of the transactions contemplated by the Stock Purchase Agreement, the Investor Rights Agreement became effective and the Company and Novartis executed a research collaboration and license agreement (the "Collaboration and License Agreement") (collectively the "Novartis Agreements").

Under the terms of the Stock Purchase Agreement, on October 12, 2005, Novartis purchased 5,267,865 shares of the Company's common stock at a purchase price of $11.11 per share for an aggregate purchase price of approximately $58.5 million, which, after such issuance, represented 19.9% of the Company's outstanding common stock as of the date of issuance.

Under the terms of the Investor Rights Agreement, the Company granted Novartis demand and piggyback registration rights under the Securities Act of 1933, as amended, for the shares acquired by Novartis. The Company also granted to Novartis rights to acquire additional equity securities of the Company in the event that the Company proposes to sell or issue any equity securities of the Company, subject to specified exceptions, as described in the Investor Rights Agreement, such that Novartis would be able to maintain its ownership percentage in the Company. Novartis agreed, until the later of (1) three years from the date of the Investor Rights Agreement and (2) the date of termination or expiration of the Selection Term (as defined in the Collaboration and License Agreement), not to acquire any securities of the Company (other than an acquisition resulting in Novartis and its affiliates beneficially owning less than 20% of the total outstanding voting securities of the Company), participate in any tender or exchange offer, merger or other business combination involving the Company or seek to control or influence the management, Board of Directors or policies of the Company, subject to specified exceptions described in the Investor Rights Agreement.

Under the terms of the Collaboration and License Agreement, the parties will work together on selected targets, as defined in the Collaboration and License Agreement, to discover and develop therapeutics based on RNA interference ("RNAi"). The Collaboration and License Agreement has an initial term of three years and may be extended for two additional one-year terms at the election of Novartis. In addition, Novartis may terminate the Collaboration and License Agreement after a period of two years under certain circumstances or in the event that the Company materially breaches its obligations. The Company may terminate the agreement with respect to particular programs, products and or countries in the event of certain material breaches of obligations by Novartis, or in its entirety under certain circumstances for multiple such breaches. Novartis made up-front payments totaling $10.0 million to the Company in October 2005 in consideration for the rights granted to Novartis under the Collaboration and License Agreement and to reimburse prior costs incurred by the Company to develop *in vivo* RNAi technology. In addition, the Collaboration and License Agreement includes terms under which Novartis will provide the Company with research funding and milestone payments as well as royalties on annual net sales of

products resulting from the Collaboration and License Agreement. The Collaboration and License Agreement also provides Novartis with a non-exclusive option to integrate the Company's intellectual property relating to certain RNAi technology into Novartis' operations under certain circumstances (the "Integration Option"). In connection with the exercise of the Integration Option, Novartis will be required to make certain additional payments to the Company. The terms of the Collaboration and License Agreement allow the Company to retain the right to discover, develop, commercialize or manufacture compounds that function through the mechanism of RNAi or products that contain such compounds as an active ingredient with respect to targets not selected by Novartis for inclusion in the Collaboration and License Agreement provided that Novartis has a right of first offer in the event that the Company proposes to enter into an agreement with a third party with respect to any such target. The Company recognized approximately $0.7 million in revenues during 2005 under the Novartis Agreements and has $16.1 million of deferred revenue on its balance sheet related to this agreement at December 31, 2005.

Novartis Pandemic Flu Alliance

In February 2006, the Company entered into an alliance with Novartis for the development of RNAi therapeutics for pandemic flu ("Novartis Flu Agreement"). The Novartis Flu Agreement supplements and, to the extent described therein, supersedes in relevant part the collaboration and license agreement for the broad Novartis alliance. Under the terms of the Novartis Flu Agreement, the Company and Novartis have joint responsibility for development of RNAi therapeutics for pandemic flu. Novartis will have primary responsibility for commercialization of such RNAi therapeutics worldwide, but the Company will be actively involved, and may in certain circumstances take the lead, in commercialization in the United States. The Company is eligible to receive significant funding from Novartis for its efforts on RNAi therapeutics for pandemic flu, and to receive a significant share of any profits.

Garching Innovation GmbH License Agreement

In December 2002, the Company entered into a co-exclusive license with Garching for the worldwide rights to use and sublicense certain patented technology to develop and commercialize therapeutic products and related applications. The Company also obtained the rights to use, without the right to sublicense, the technology for all diagnostic uses other than for the purposes of therapeutic monitoring. In consideration for the rights to license this technology, the Company agreed to issue to Garching shares of Series B redeemable convertible preferred stock. As of December 31, 2002, the Company valued this consideration at the Series B redeemable convertible preferred stock issuance price of $2.50 per share for total consideration of $1.8 million. The Company recorded the consideration as license fee expense during the period from inception (June 14, 2002) through December 31, 2002 as the technology had not reached technological feasibility and does not have any alternative future use. In July 2003, the Company formally issued the 723,240 shares of Series B redeemable preferred stock to Garching. The Company will also be required to pay future royalties on net sales of all therapeutic and prophylactic products developed with the technology.

The Company was also given the ability to acquire the remaining 50 percent exclusive rights to the technology that had not been previously granted to the Company by Garching upon the establishment of a German-based company with comparable operational work force and resources. The Company successfully obtained the remaining 50 percent exclusive rights upon the acquisition of Ribopharma AG in July 2003 (Note 3) and in consideration for the remaining rights to this technology, issued 158,605 shares of Series B redeemable convertible preferred stock, which were converted into 83,476 shares of common stock upon the closing of the Company's initial public offering in June 2004. These shares were determined to have a fair value of $0.4 million and the value was recorded as license fee expense in 2003. The Company is also reserving an additional 8,594 shares of its common stock which is contingently issuable if a specified claim is obtained related to one of its licensed patents.

In June 2005, the Company entered into an amendment agreement with Garching Innovation GmbH ("Garching"). This amendment eliminated the requirement that the Company maintain operations in Germany

that are comparable to its operations in the United States and replaced this provision with a requirement that the Company maintain a minimum level of employees in Germany until December 2007. This amendment secures the Company's exclusivity to use and sublicense certain patented technology to develop and commercialize therapeutic products and related applications. In connection with this amendment, the Company issued 270,000 shares of its common stock, which was valued at $2.1 million, to Garching and certain of its affiliated entities. The Company recorded the consideration as license fee expense for the year ended December 31, 2005, as the technology had not reached technological feasibility and does not have any alternative future uses.

Isis Pharmaceuticals, Inc. Collaboration and License Agreement

In March 2004, the Company entered into a collaboration and license agreement with Isis Pharmaceuticals, Inc. ("Isis"). Isis granted the Company licenses to its current and future patents and patent applications relating to chemistry and to RNA-targeting mechanisms for the research, development and commercialization of double-stranded RNA products. The Company has the right to use Isis technologies in its development programs or in collaborations and Isis has agreed not to grant licenses under these patents to any other organization for the discovery, development and commercialization of double-stranded RNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. The Company granted Isis non-exclusive licenses to its current and future patents and patent applications relating to RNA-targeting mechanisms and to chemistry for research use. The Company also granted Isis the exclusive or co-exclusive right to develop and commercialize double-stranded RNA products developed using RNAi technology against a limited number of targets. In addition, the Company granted Isis non-exclusive rights to research, develop and commercialize single-stranded RNA products.

Under the terms of the agreement, the Company agreed to pay Isis an upfront license fee of $5.0 million, $3.0 million of which was paid upon signing of the agreement and the remaining $2.0 million of which was paid in January 2005. The Company recorded the initial $5.0 million of consideration as license fee expense within research and development costs during the year ended December 31, 2004 as the technology had not reached technological feasibility and does not have any alternative future use. The Company also agreed to make milestone payments, payable upon the occurrence of specified development and regulatory events, and royalties to Isis for each product that the Company or a collaborator develops utilizing Isis intellectual property. In addition, the Company agreed to pay to Isis a percentage of certain fees earned from strategic collaborations it may enter into that include access to the Isis intellectual property. In conjunction with the agreement, Isis purchased 1,666,667 shares of Series D preferred stock of the Company for $10.0 million, which were converted into 877,193 shares of common stock upon the closing of the Company's initial public offering in June 2004. Isis also agreed to pay the Company a license fee, milestone payments, payable upon the occurrence of specified development and regulatory events, and royalties for each product developed by Isis or a collaborator that utilizes the Company's intellectual property. The agreement also gives the Company an option to use Isis manufacturing services for RNA-based therapeutics. In connection with the Merck ocular collaboration signed in June 2004, which is discussed below, the Company recorded $0.5 million in license fee expense related to payments due to Isis. In October 2005, as a result of certain payments received by the Company in connection with the Novartis Agreements, the Company made payments totaling approximately $3.7 million to Isis.

In addition, the agreement with Isis gives the Company the exclusive right to grant sub-licenses for Isis technology to third parties with whom the Company is not collaborating. The Company may include these sub-licenses in its InterfeRx licenses and research reagent and services licenses. If a license includes rights to Isis intellectual property, the Company will share revenues from that license equally with Isis.

If, by January 1, 2008, the Company or a collaborator has not completed the studies required for an investigational new drug application filing or similar foreign filing for at least one product candidate involving these patent rights, Isis would have the right to grant licenses to third parties for the patents and patent applications licensed to the Company, thereby making the Company's rights non-exclusive.

Collaboration Agreement with Merck & Co.

In September 2003, the Company entered into a five-year strategic alliance with Merck to develop RNAi-based technology and therapeutics. For technology development, Merck and the Company each committed to devote resources, including full-time equivalents and expertise, to the collaborative development of advanced RNAi technology. Merck will have rights to use this technology solely for the identification and validation of drug targets; the Company will have rights to use it for these purposes and also for therapeutic purposes. For therapeutics development, Merck agreed to provide the Company with twelve proprietary drug targets as potential targets for siRNA therapeutics. The Company has the right, but not the obligation, to develop siRNA drug candidates against each target provided by Merck. If the Company advances a candidate to a defined point in pre-clinical development, the Company and Merck will then decide whether the Company, Merck or the two companies together will proceed with the further development and commercialization of that candidate. For each drug candidate in whose development Merck decides to participate, it will make a cash payment to the Company at the time of its decision, and will also reimburse the Company for a portion of the costs the Company has so far incurred on that candidate.

In connection with this alliance, Merck made an upfront cash payment of $2.0 million and a $5.0 million equity investment in the Company during 2003. In addition, in connection with this agreement, the Company received $1.0 million in additional license fee payments from Merck in September 2004 and September 2005 and $7.0 million in December 2004 upon the attainment of a pre-specified technology milestone. Of the $7.0 million received in December 2004, $5.0 million was from the sale of 710,273 shares of the Company's common stock and $2.0 million represented a cash milestone. The Company is recognizing the revenue related to the up-front and license payments ratably over the estimated period of performance under the agreement, which the Company has determined to be six years, and recognized the cash milestone as revenue upon receipt. The amortization of these payments resulted in revenues of $0.9 million, $0.6 million and $0.1 million in 2005, 2004 and 2003, respectively. Of the $7.0 million payment received in December 2004, the Company recorded $5.3 million in stockholders' equity for the sale of common stock, which represents the fair value of the stock on the date of issuance, and recognized the residual of $1.7 million of revenue in connection with the cash milestone payment. As of December 31, 2005, the Company has deferred revenue on its balance sheet of $2.4 million.

Merck Ocular Collaboration

In June 2004, the Company entered into a collaboration and license agreement with Merck. The agreement is a multi-year collaboration to develop and commercialize RNAi therapeutics for ocular diseases. This collaboration has been focused on age-related macular degeneration ("AMD") and other ocular diseases caused by abnormal growth or leakage of small blood vessels in the eye. The Company's existing program to develop a Direct RNAi™ therapeutic for the treatment of AMD was incorporated into this collaboration.

Under the terms of the agreement, the Company received a $2.0 million license fee from Merck as well as $1.0 million representing reimbursement of prior research and development costs incurred by the Company. These up-front amounts were deferred and are being recognized as revenue over the estimated period of performance under the collaboration agreement, which the Company has determined to be eight years. In addition, the agreement provides for the Company to work on two additional mutually agreed ocular targets. Merck and the Company will jointly fund the development of, and share the profits from, any RNAi therapeutics for the United States market that result from the collaboration. The Company will also have the option to co-promote these RNAi therapeutics in the United States. Marketing and sales outside of the United States will be conducted by Merck, with the Company receiving royalties. During the years ended December 31, 2005 and 2004, the Company recorded net cost reimbursement revenues of $2.2 million and $1.5 million, respectively, which represent $2.5 million and $1.8 million, respectively, of research and development costs to be reimbursed by Merck under the terms of the agreement less $0.3 million and $0.3 million, respectively, of research and development costs to be reimbursed by the Company to Merck. The Company also recorded revenues of $0.5 million and $0.3 million for the year ended

December 31, 2005 and 2004, respectively, from the amortization of the up-front payments received from Merck and has $2.3 million of deferred revenue on its balance sheet related to this agreement at December 31, 2005.

Medtronic, Inc.

In February 2005, the Company entered into a strategic alliance with Medtronic to pursue the development of therapeutics for the treatment of neurodegenerative disorders such as Huntington's, Alzheimer's and Parkinson's disease. The collaboration is focused on developing novel drug-device combinations incorporating RNAi therapeutics. Initially, the Company and Medtronic are engaged in a joint technology development program for a period of two years, a period that can be extended by mutual agreement. This initial joint technology development program is focused on delivering candidate RNAi therapeutics to specific areas of the brain using an implantable infusion system.

After successful completion of the initial joint technology development program and a joint decision to initiate product development, the Company would be responsible for the discovery and early development of candidate RNAi therapeutics, and Medtronic would be responsible for late-stage development and commercialization of any drug-device products that result. Medtronic also would adapt or develop medical devices to deliver the candidate RNAi therapeutics to targeted locations in the nervous system.

After successful completion of the initial joint technology development program and a joint decision to initiate product development, Medtronic would make an initial equity investment in the Company and could make additional investments upon successful completion of specified milestones. The aggregate amount of common stock of the Company that Medtronic would purchase if a joint decision were taken to initiate product development and the specified milestones were successfully completed would be $21.0 million. The amount of the investment to be made at the time of the joint decision to initiate product development would be between $1.0 million and $8.0 million, as determined by the Company, at the then-current market price. For the purpose of this investment, the then-current market price would be equal to the twenty-day trailing average of the closing price of common stock of the Company on the Nasdaq National Market at the end of the trading day two trading days prior to the date of the decision to initiate product development. The remaining investments would be made upon the achievement of the specified milestones at a purchase price equal to 120% of the then-current market price, calculated as just described. If either Medtronic or the Company decides not to initiate product development under the collaboration agreement, Medtronic would not be required to make any equity investment in the Company.

After successful completion of the initial joint technology development program and a joint decision to initiate product development, the Company would also be eligible to receive additional cash milestone payments for each product developed and royalties on sales of any RNAi therapeutic component of novel drug-device combinations that result from the collaboration.

Cystic Fibrosis Foundation Therapeutics, Inc.

In March 2005, the Company entered into a collaboration with Cystic Fibrosis Foundation Therapeutics, Inc. ("CFFT") to investigate the potential for RNAi therapeutics to treat cystic fibrosis ("CF"). Under this collaboration, CFFT provided the Company with an initial payment of $0.5 million and a milestone payment of $0.3 million and may make additional payments totaling an aggregate of $0.7 million in the event that certain scientific milestones are achieved. In addition to funding, CFFT will provide the Company with access to certain scientific resources to support the Company's siRNA discovery and development efforts. If the discovery and development efforts under this collaboration result in the identification of siRNAs that are candidates for further development, the parties may negotiate a mutually agreeable support arrangement for further phases of development. In the event that the Company develops a marketable therapeutic for the treatment of CF, the Company will be required to pay CFFT certain pre-determined payments. The Company recognizes revenues under this collaboration based on the proportionate performance of work completed in relation to estimates of the total work to be performed under the collaboration, with revenues limited to the amount of non-refundable cash received. The Company recognized

revenues of $0.8 million for the year ended December 31, 2005. The Company has no deferred revenue on its balance sheet related to this agreement at December 31, 2005.

InterfeRx and Research Reagent Licenses

The Company has entered into agreements whereby it licenses its intellectual property to others for the development and commercialization of RNAi therapeutics relating to specific protein targets outside of the Company's strategic focus ("InterfeRx Licenses"). In addition to its InterfeRx Licenses, the Company has granted licenses to its intellectual property for the development and commercialization of research reagents and services. During 2005, the Company recognized revenues of $0.6 million from these programs.

13. QUARTERLY FINANCIAL DATA (UNAUDITED)

The following information has been derived from unaudited consolidated financial statements that, in the opinion of management, include all recurring adjustments necessary for a fair presentation of such information.

	Three Months Ended			
	March 31, 2005	June 30, 2005	September 30, 2005	December 31, 2005
	(In thousands, except per share data)			
Revenues	$ 1,643	$ 1,108	$ 1,413	$ 1,552
Operating expenses	8,324	12,312	12,083	16,469
Net loss	(6,600)	(11,145)	(10,678)	(14,491)
Net loss per common share — basic and diluted	$ (0.32)	$ (0.54)	$ (0.51)	$ (0.56)
Weighted average shares — basic and diluted	20,435	20,606	20,914	25,731

	Three Months Ended			
	March 31, 2004	June 30, 2004	September 30, 2004	December 31, 2004
	(In thousands, except per share data)			
Revenues	$ 134	$ 131	$ 1,367	$ 2,646
Operating expenses	13,466	7,106	7,793	8,177
Net loss	(13,582)	(6,956)	(6,416)	(5,700)
Net loss attributable to common stockholders	(15,544)	(7,707)	(6,416)	(5,700)
Net loss per common share — basic and diluted	$ (9.39)	$ (1.10)	$ (0.33)	$ (0.29)
Weighted average shares — basic and diluted	1,655	6,997	19,507	19,614

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Our management, with the participation of our chief executive officer and vice president of finance and treasurer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2005. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31 2005, the Company's chief executive officer and vice president of finance and treasurer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's report on our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) and the independent registered public accounting firm's related audit report are included in Item 8 of this Form 10-K and are incorporated herein by reference.

No change in our internal control over financial reporting occurred during the fiscal quarter ended December 31, 2005 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS AND EXECUTIVE OFFICERS OF THE REGISTRANT

We will file with the Securities and Exchange Commission a definitive Proxy Statement, which we refer to herein as the Proxy Statement, not later than 120 days after the close of the fiscal year ended December 31, 2005. The information required by this item is incorporated herein by reference to the information contained under the sections captioned "Proposal One — Election of Class II Directors," "Section 16(a) Beneficial Ownership Reporting Compliance" and "Corporate Governance" of the Proxy Statement. The information required by this item relating to executive officers is included in "Part I, Item 1 — Business- Executive Officers of the Registrant" of this Annual Report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this item is incorporated herein by reference to the information contained under the sections captioned "Executive Compensation," "Compensation of Directors," "Compensation Committee Interlocks and Insider Participation" and "Employment Arrangements" of the Proxy Statement.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this item is incorporated herein by reference to the information contained under the sections captioned "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information" of the Proxy Statement.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS

The information required by this item is incorporated herein by reference to the information contained under the sections captioned "Employment Arrangements" and "Certain Relationships and Related Transactions" of the Proxy Statement.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this item is incorporated herein by reference to the information contained under the sections captioned "Principal Accountant Fees and Services" and "Pre-Approval Policies and Procedures" of the Proxy Statement.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) (1) Financial Statements

The following consolidated financial statements are filed as part of this report under "Item 8 — Financial Statements and Supplementary Data":

(a) (2) List of Schedules

Schedule II — Valuation and Qualifying Accounts for the years ended December 31, 2005, 2004 and 2003.

All other schedules to the consolidated financial statements are omitted as the required information is either inapplicable or presented in the consolidated financial statements.

(a) (3) List of Exhibits

The exhibits which are filed with this report or which are incorporated herein by reference are set forth in the Exhibit Index hereto.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized, on March 16, 2006.

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ John M. Maraganore, Ph.D.
John M. Maraganore, Ph.D.
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, the Report has been signed below by the following persons on behalf of the Registrant and in the capacities indicated as of March 16, 2006.

Name	Title
/s/ John M. Maraganore, Ph.D. John M. Maraganore, Ph.D.	Director and President and Chief Executive Officer (Principal Executive Officer)
/s/ Patricia L. Allen Patricia L. Allen	Vice President of Finance and Treasurer (Principal Financial and Accounting Officer)
/s/ Peter Barrett, Ph.D. Peter Barrett, Ph.D.	Director
/s/ John K. Clarke John K. Clarke	Director
/s/ Vicki L. Sato Vicki L. Sato	Director
/s/ Paul R. Schimmel, Ph.D. Paul R. Schimmel, Ph.D.	Director
/s/ Phillip A. Sharp, Ph.D. Phillip A. Sharp, Ph.D.	Director
/s/ Kevin P. Starr Kevin P. Starr	Director
/s/ James L. Vincent James L. Vincent	Director

SCHEDULE II

ALNYLAM PHARMACEUTICALS, INC.
VALUATION AND QUALIFYING ACCOUNTS
(In thousands)

Year	Description	Balance at Beginning of Period	Additions	Deductions	Balance at End of Period
2005:	DEFERRED TAX ASSET VALUATION ALLOWANCE	$21,135	$16,855	$300	$37,690
2004:	DEFERRED TAX ASSET VALUATION ALLOWANCE	$ 8,917	$12,218	$ —	$21,135
2003:	DEFERRED TAX ASSET VALUATION ALLOWANCE	$ 862	$ 8,055	$ —	$ 8,917

EXHIBIT INDEX

Exhibit No.	Exhibit
3.1	Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
3.2	Amended and Restated Bylaws of the Registrant (filed as Exhibit 3.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.1	Specimen certificate evidencing shares of common stock (filed as Exhibit 4.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.2	Rights Agreement dated as of July 13, 2005 between the Registrant and EquiServe Trust Company, N.A., as Rights Agent, which includes as Exhibit A the Form of Certificate of Designations of Series A Junior Participating Preferred Stock, as Exhibit B the Form of Rights Certificate and as Exhibit C the Summary of Rights to Purchase Preferred Stock (as Exhibit 4.1 to the Registrant's Current Report on Form 8-K filed on July 14, 2005 (File No. 000-50743) and incorporated herein by reference)
10.1*	2002 Employee, Director and Consultant Stock Plan, as amended, together with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.2*	2003 Employee, Director and Consultant Stock Plan, as amended, together with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.3*	2004 Stock Incentive Plan, as amended (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on June 10, 2005 (File No. 000-50743) and incorporated herein by reference)
10.4*	Forms of Incentive Stock Option Agreement and Nonstatutory Stock Option Agreement under 2004 Stock Incentive Plan, as amended (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
10.5*	Form of Nonstatutory Stock Option Agreement under 2004 Stock Incentive Plan granted to John M. Maraganore, Ph.D., on December 21, 2004 (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on December 28, 2004 (File No. 000-50743) and incorporated herein by reference)
10.6*	Form of Nonstatutory Stock Option Agreement under 2004 Stock Incentive Plan granted to James L. Vincent on July 12, 2005 (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on July 13, 2005 (File No. 000-50743) and incorporated herein by reference)
10.7*	Form of Restricted Stock Agreement under 2004 Stock Incentive Plan issued to James L. Vincent on July 12, 2005 (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on July 13, 2005 (File No. 000-50743) and incorporated herein by reference)
10.8*	2004 Employee Stock Purchase Plan (filed as Exhibit 10.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.9*	Summary of Cash Compensation For Directors (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on June 10, 2005 (File No. 000-50743)) and incorporated herein by reference)
10.10	Registration Rights Agreement dated as of July 31, 2003 and amended as of October 9, 2003 and February 26, 2004 by and among the Registrant and the parties listed on Schedule A thereto (filed as Exhibit 10.5 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.11	Investor Rights Agreement dated as of September 8, 2003 and amended on February 26, 2004 by and between the Registrant and Merck & Co., Inc. (filed as Exhibit 10.6 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.12	Investor Rights Agreement entered into as of March 11, 2004 by and between the Registrant and Isis Pharmaceuticals, Inc. (filed as Exhibit 10.25 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)

Exhibit No.	Exhibit
10.13	Stock Purchase Agreement, dated as of September 6, 2005, by and between the Registrant and Novartis Pharma AG (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on September 12, 2005 (File No. 000-50743) and incorporated herein by reference)
10.14	Investor Rights Agreement, dated as of September 6, 2005, by and between the Registrant. and Novartis Pharma AG (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on September 12, 2005 (File No. 000-50743) and incorporated herein by reference)
10.15*	Letter Agreement between the Registrant and John M. Maraganore, Ph.D. dated October 30, 2002 (filed as Exhibit 10.7 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.16*	Letter Agreement between the Registrant and Vincent J. Miles, Ph.D. dated June 16, 2003 (filed as Exhibit 10.8 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.17*	Letter Agreement between the Registrant and Thomas R. Ulich, M.D. dated June 15, 2003 (filed as Exhibit 10.9 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.18*	Letter Agreement between the Registrant and Barry E. Greene dated September 29, 2003 (filed as Exhibit 10.10 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.19	Loan and Security Agreement by and between Lighthouse Capital Partners V, L.P. and the Registrant dated as of March 26, 2004, together with the Negative Pledge Agreement by and between Lighthouse Capital Partners V, L.P. and the Registrant dated as of March 26, 2004 (filed as Exhibit 10.11 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.20	Amendment No. 1 dated August 2, 2004 to Loan and Security Agreement dated as of March 26, 2004 by and between the Registrant and Lighthouse Capital Partners V, L.P. (filed as Exhibit 10.6 to the Registrant's Quarterly Report on Form 10-Q (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
10.21	Amendment No. 02 dated June 20, 2005 to Loan and Security Agreement dated as of March 26, 2004, as amended, by and between the Registrant and Lighthouse Capital Partners V, L.P. (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on June 24, 2005 (File No. 000-50743) and incorporated herein by reference)
10.22	Warrants to Purchase Preferred Stock effective as of March 30, 2004 issued to Lighthouse Capital Partners V, L.P. and Lighthouse Capital Partners IV, L.P. (filed as Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.23	Lease, dated as of September 26, 2003 by and between the Registrant and Three Hundred Third Street LLC (filed as Exhibit 10.15 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.24†	License Agreement between Cancer Research Technology Limited and Alnylam U.S., Inc. dated July 18, 2003 (filed as Exhibit 10.16 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.25†	License Agreement between the Carnegie Institution of Washington and Alnylam Europe, AG, effective March 1, 2002, as amended by letter agreements dated September 2, 2002 and October 28, 2003 (filed as Exhibit 10.17 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.26†	License Agreement by and between the Cold Spring Harbor Laboratory and Alnylam U.S., Inc. dated December 30, 2003 (filed as Exhibit 10.18 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.27†	Co-exclusive License Agreement between Garching Innovation GmbH and Alnylam U.S., Inc. dated December 20, 2002, as amended by Amendment dated July 8, 2003 together with Indemnification Agreement by and between Garching Innovation GmbH and Alnylam Pharmaceuticals, Inc. effective April 1, 2004 (filed as Exhibit 10.19 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)

Exhibit No.	Exhibit
10.28†	Co-exclusive License Agreement between Garching Innovation GmbH and Alnylam Europe, AG dated July 30, 2003 (filed as Exhibit 10.20 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.29	Agreement between the Registrant, Garching Innovation GmbH, Alnylam U.S., Inc., a wholly-owned subsidiary of the Registrant, and Alnylam Europe AG, a wholly-owned subsidiary of the Registrant, dated June 14, 2005 (filed as Exhibit 10.8 to the Registrant's Quarterly Report on Form 10-Q (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
10.30†	Agreement between The Board of Trustees of the Leland Stanford Junior University and Alnylam U.S., Inc. effective as of September 17, 2003 (filed as Exhibit 10.21 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.31†	Research Collaboration and License Agreement by and among Merck & Co., Inc., Alnylam U.S., Inc. and Registrant dated September 8, 2003 (filed as Exhibit 10.22 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.32†	Sponsored Research Agreement among Mayo Foundation for Medical Education and Research, Mayo Clinic Jacksonville and Alnylam Pharmaceuticals, Inc. effective as of October 1, 2003 (filed as Exhibit 10.23 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.33†	Strategic Collaboration and License Agreement effective as of March 11, 2004 between Isis Pharmaceuticals, Inc. and the Registrant (filed as Exhibit 10.24 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.34	Agreement between the Registrant and Perini Building Company, Inc. effective as of March 26, 2004 (filed as Exhibit 10.26 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.35†	Collaboration and License Agreement by and among Merck and Co., Inc. and the Registrant effective as of June 29, 2004 (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 000-50743) for the quarterly period ended June 30, 2004 and incorporated herein by reference)
10.36†	Collaboration Agreement by and among Medtronic, Inc. and the Registrant effective as of February 8, 2005 (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 000-50743) for the quarterly period ended March 31, 2005 and incorporated herein by reference)
10.37†	Research Collaboration and License Agreement effective as of October 12, 2005 by and between the Registrant and Novartis Institutes for BioMedical Research, Inc. (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on October 12, 2005 (File No. 000-50743) and incorporated herein by reference)
10.38†	Addendum Re: Influenza Program to Research Collaboration and License Agreement, dated February 17, 2006, by and between the Registrant and Novartis Institutes for BioMedical Research, Inc. (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on February 24, 2006 (File No. 000-50743) and incorporated herein by reference).
10.39#	Amendment No. 1 to Addendum Re: Influenza Program to Research Collaboration and License Agreement, effective as of March 14, 2006, by and between the Registrant and Novartis Institutes for BioMedical Research, Inc.
21.1#	Subsidiaries of the Registrant
23.1#	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm
31.1#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)-14(a)/15d-14(a), by Chief Executive Officer
31.2#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)-14(a)/15d-14(a), by Vice President of Finance and Treasurer
32.1#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Chief Executive Officer
32.2#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Vice President of Finance and Treasurer

* Management contracts or compensatory plans or arrangements required to be filed as an exhibit hereto pursuant to Item 15(a) of Form 10-K.

† Indicates confidential treatment requested as to certain portions, which portions were omitted and filed separately with the Securities and Exchange Commission pursuant to a Confidential Treatment Request.

Filed herewith

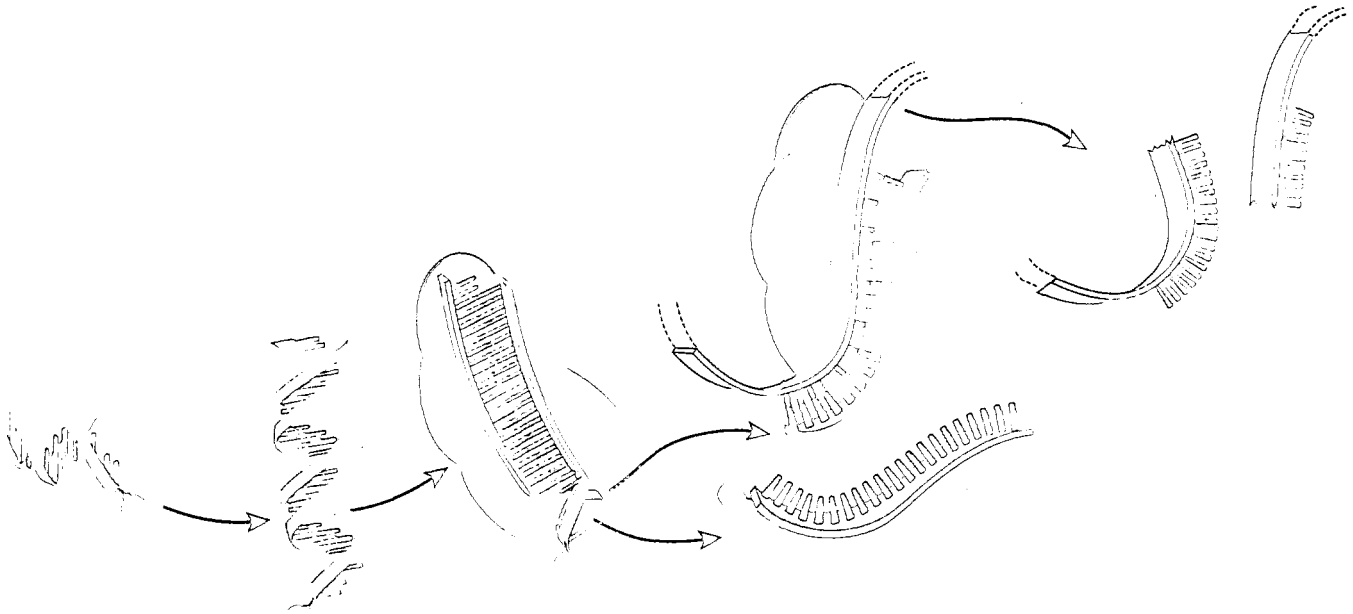
Alnylam is Realizing the Potential of RNAi in Our Efforts to Create an Entirely New Class of Drugs Designed to Treat Human Diseases in a Fundamentally New Way.

2005 was a transformational year for us, one in which we achieved many important milestones towards our goal of building a significant biopharmaceutical company.

At Alnylam, we are making major advances in translating the science of RNAi into a product platform capable of delivering an innovative and robust product pipeline.

An important event for Alnylam – and for the field of RNAi – was the initiation of human clinical testing of our lead product candidate, ALN-RSV01, for the treatment of respiratory syncytial virus infection. ALN-RSV01 is the first RNAi therapeutic in clinical development for an infectious disease.

In addition, in 2005, we saw significant momentum in our partnering efforts resulting in important pharmaceutical collaborations with Novartis and Medtronic. We expect these alliances and our continuing Merck collaborations to advance development of RNAi therapeutics for a wide range of disease areas.



TO OUR STOCKHOLDERS

2005 was a transformational year for Alnylam in our steadfast efforts to realize the potential of RNA interference, or RNAi. RNAi therapeutics represent an opportunity to create a whole new class of drugs that treat disease in a fundamentally new way. With this opportunity, we are focused on building a leading biopharmaceutical company. The following is a review of our important recent achievements and our views as to how they relate directly to the creation of stockholder value.

I'd like to reiterate Alnylam's vision and mission, which are at the core of our value creation strategy. Our vision *"to harness a revolution in biology for human health"* represents our belief that RNAi is an important and very rare discontinuity in biology that can have broad impact for the treatment of human disease. This opportunity enables our mission of *"building a leading product company founded on RNAi."* Indeed, we believe that we can create a new biopharmaceutical company such as those that emerged in the late 1970's from the early pioneers of the biotechnology industry. We were honored earlier this year to receive our industry's most prestigious award, the James D. Watson Helix Award, for outstanding corporate achievement. We are grateful to our biotech peers for their acknowledgement of our bold vision for new innovations in medicine, and our execution on our mission in building a leading biopharmaceutical company.

The promise of RNAi is to harness this powerful natural pathway, which exists in all of our cells, to create a new approach for the treatment of disease using therapeutic gene silencing. The progress in this field has been remarkable when one considers that RNAi began as an observation in petunias and worms in the 1990's and that the first published evidence of its activity in mammalian systems by our co-founder Dr. Thomas Tuschl only occurred in 2001. The translation of these scientific breakthroughs into a drug discovery capability has in fact been led by Alnylam scientists. In late 2004, we published a landmark paper in one of the world's leading scientific journals, *Nature,* showing the ability to introduce drug-like properties into small interfering RNAs, or siRNAs, the molecules that mediate RNAi, to achieve therapeutic gene silencing in mice. We then extended these efforts recently to demonstrate clear therapeutic efficacy for systemically delivered siRNAs in primates, results which were also published in *Nature*. These advancements and our capabilities have truly widened the eyes of academic and clinical opinion leaders around the world and have captured the attention of heads of major pharmaceutical and top-tier biotechnology companies. We are proud of our scientific team for their commitment to scientific excellence through publications and presentations in peer-reviewed meetings or journals. Most importantly, these scientific accomplishments bring hope to patients who see new promise for treatments of diseases that cannot be addressed with today's drugs.

We began 2005 as a pre-clinical company and we ended the year as a clinical company with an exciting RNAi therapeutic for the treatment of respiratory syncytial virus (RSV) infection in Phase I clinical trials. We believe that ALN-RSV01 can become a breakthrough therapy for what is today's leading cause of pediatric hospitalization in the U.S. and a major infection in several adult populations. Building on our success in moving the first RNAi therapeutic for the treatment of viral disease into human studies, we are working with our partners at Novartis on another important viral disease, developing a broadly acting anti-viral treatment for flu that could be used as part of government stockpiles for pandemic preparedness. Further, we have a number of additional efforts to harness RNAi for the treatment of diseases ranging from cystic fibrosis to Huntington's disease. Overall, our pipeline strategy is designed to maximize value creation as we build our business. First, we are focused on well-validated disease targets that existing drugs cannot address, to create a truly innovative pipeline that we believe will be recognized by patients, physicians, and partners. Next, our pipeline balances proprietary "Alnylam owned" programs with those that are partnered in co-development/profit-sharing or milestone/royalty-based arrangements, creating the appropriate balance of downstream value retention with upstream risk-sharing. Finally, we are building a pipeline with "multiple shots on goal" that we believe is the way to create a long-term sustainable business in our industry.

JOHN M. MARAGANORE, PH.D.
President and Chief Executive Officer

From the start, Alnylam was focused on a strategy to proactively consolidate the necessary intellectual property (IP) to develop and commercialize RNAi therapeutics, and we believe this strategy is enabling us to build the greatest possible value from the emergence of a whole new class of drugs; imagine the potential of building a monoclonal antibody company where the pioneering patents (e.g., Winter, Boss, Cabilly, and Queen) were held by one company. From the beginning of 2005, we evidenced dramatic strengthening of Alnylam's IP position, where across "fundamental," chemistry, and target categories of IP, we received several broad patent grants from the European Patent Office and allowed patents from the U.S. Patent and Trademark Office. Only Alnylam has rights to these patents for RNAi therapeutics. Importantly, our recently allowed "Tuschl II" patents include the first and only claim sets that broadly cover the critical features of siRNAs, including their chemical modification and their targeting of all mammalian disease targets. This rich IP estate is being leveraged today to build value for Alnylam. IP has been a critical asset in forging five relationships with three major pharmaceutical companies, resulting in over $100 million of funding to date from our alliances, and in licensing these assets in certain non-strategic areas to over 20 additional companies who acknowledge the strength of our IP for commercializing RNAi products. Our IP has therefore helped to generate substantial capital that we can reinvest in the development of our products and to sustain the product exclusivity needed for innovative medicines to be brought to market.

A clear business highlight for 2005 was the landmark alliance we forged with Novartis, a world-leading global pharmaceutical company dedicated to innovation-based medicines. We believe that this alliance is one of the most significant drug discovery partnerships in biotechnology, and marks a transforming event in building our business. Indeed, the scale and scope of this relationship broadens our partnered pipeline of RNAi therapeutics and also enables Alnylam to advance its own pipeline to later stages of development and to the market. We also formed a number of other important alliances including: Medtronic to combine RNAi therapeutics with cutting-edge device technology for delivery to the nervous system so as to create disease-modifying therapies for major neurodegenerative diseases; the Cystic Fibrosis (CF) Foundation to discover RNAi therapeutics that could potentially rescue the genetic defect in CF; and, in a separate co-development/profit-sharing arrangement again with Novartis, to discover and develop RNAi therapeutics for pandemic flu. Alliances with major pharmaceutical companies and other partners are a critical element of our business strategy as they bring together expertise, capabilities, and funding to advance RNAi therapeutics to patients and the market. We are fortunate to have assembled such a team of new partners that join Merck and Isis, our partners in pioneering relationships formed in 2003 and 2004.

Of course, all of our progress above stems from the efforts of our employees and directors who have a passion and commitment to create a new class of drugs and a significant new company. During the year, we strengthened this team with the addition of top-quality scientists in biology, chemistry, and development functions and new directors to our Board with operating experience in building innovation-based pipelines and top-tier leading biopharmaceutical companies.

In closing, I'd like to thank you, our stockholders, for your interest and support of Alnylam's efforts.
We believe that we are building a very special company and we are delighted to have you as part of our future.

John M. Maraganore, Ph.D., President and Chief Executive Officer

Receives $7 Million Milestone Payment for Scientific Progress from Merck

Initiates RNAi Therapeutic Development Program for Respiratory Syncytial Virus Infection

Grants InterfeRx™ License to GeneCare Research Institute for Oncology Targets

Initiates Spinal Cord Injury Program as Part of Therapeutic Alliance with Merck

Signs Manufacturing Agreement with Dowpharma℠ for RNAi Therapeutics

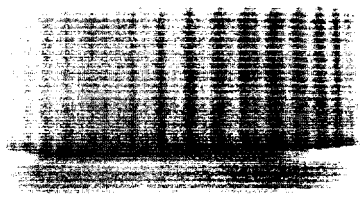
01.03.05 | 01.04.05 | 01.06.05 | 01.25.05 | 02.09.05 | 03.16.05 | 03.29.05

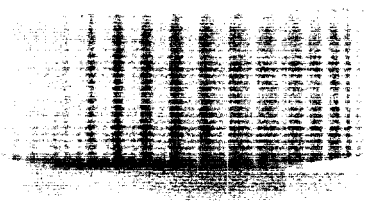
Medtronic and Alnylam Collaborate on Potential Treatments for Major Neurodegenerative Diseases

Neurodegenerative diseases such as Huntington's, Alzheimer's and Parkinson's afflict an estimated 17 million people worldwide. We believe that RNAi therapeutics have real potential to treat these diseases in a fundamentally new way. Our collaboration will pursue development of novel drug-device combinations that incorporate RNAi therapeutics and provide Alnylam with access to leading device technology for the delivery of its innovative treatments for neurodegenerative disorders.

Cystic Fibrosis Foundation Therapeutics (CFFT) and Alnylam Initiate Collaboration to Discover RNAi Therapeutic to Treat Cystic Fibrosis

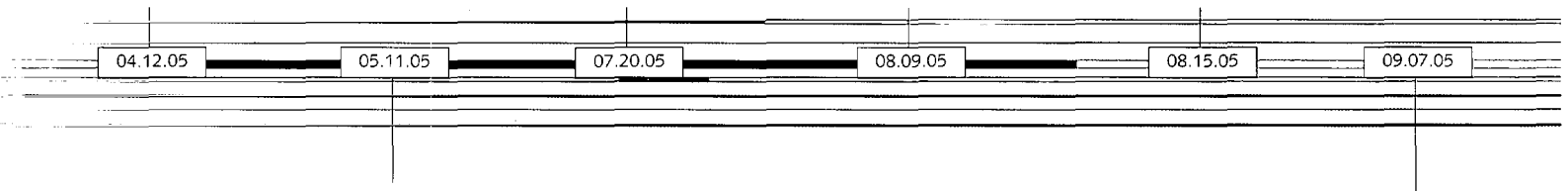
Cystic fibrosis (CF) is a genetic disease which leads to life-threatening lung infections and affects approximately 30,000 people in the U.S. Alnylam and the CFFT, the drug development arm of the CF Foundation, initiated a collaborative program to discover an RNAi therapeutic for the treatment of CF. The collaboration is focused on using RNAi to rescue the underlying genetic defect and restore normal lung function to patients afflicted with this disease.





STEPHEN FRIEND, PH.D.
Senior Vice President, Molecular Profiling and Cancer Research, Merck

"Merck continues to be very focused on developing innovative medicines to address significant medical issues. We recognized early on that RNAi technology has great potential for therapeutic applications and could be of tremendous value in the discovery of innovative medicines. We recognized Alnylam's leadership in developing this exciting new drug discovery platform. We continue to be encouraged by the progress we have seen to date as a result of this collaboration."



Alnylam Granted Broad European Patent Covering Compositions, Methods and Uses for RNAi Therapeutics: "Kreutzer-Limmer" Patent

We believe Alnylam has assembled the leading IP estate required for development and commercialization of RNAi therapeutics. The claims in the Kreutzer-Limmer patent are broad and cover both research and pharmaceutical commercial applications of synthetic RNAi products in the world's second largest market, Europe. We believe that this granted patent series strengthens Alnylam's IP leadership in RNAi.

Many research product suppliers have taken licenses under our IP estate, reflecting its strength. Our licenses now cover more than 50% of the market for RNAi research products and services.

Novartis and Alnylam Form Major Alliance to Discover RNAi Therapeutics

Alnylam and Novartis formed a landmark alliance in creating what we believe to be one of the most significant innovation-based collaborations in biotech and the largest alliance for RNAi therapeutics. This multi-year collaboration is focused on the discovery, development, and commercialization of innovative RNAi therapeutics across multiple therapeutic areas and brings together the leader in RNAi with one of the largest and most successful innovation-based pharmaceutical companies. Alnylam received $68.5 million in upfront consideration that included the purchase of a 19.9% equity stake in Alnylam by Novartis. Moreover, assuming successful execution of collaboration objectives, Alnylam could receive over $700 million, not including royalty payments on any commercialized products resulting from the collaboration.

STEPHEN N. OESTERLE, M.D.
Senior Vice President, Medicine and Technology, Medtronic

"Medtronic is taking a leadership role in the convergence of drugs and devices. The combination of Medtronic's proven expertise as a global leader in medical technology with Alnylam's leadership position in RNAi technology into human therapeutics, uniquely positions us to discover and develop better ways to treat serious neurodegenerative diseases. From the outset of this collaboration with Alnylam, it was clear that our respective teams were aligned on the strategy for bringing novel drug-device combinations towards development for the treatment of neurodegenerative disease, such as Huntington's and Parkinson's."

Submits IND Application to FDA for ALN-RSV01

Presents Progress with Neuropathic Pain Programs and Pre-clinical Data from Parkinson's and Huntington's Disease at 35th Annual Society for Neuroscience Meeting

NASDAQ Adds ALNY to Biotechnology Index

Announces Pandemic Flu as Next Development Program; Receives Initial Government Funding from U.S. Department of Defense's DARPA

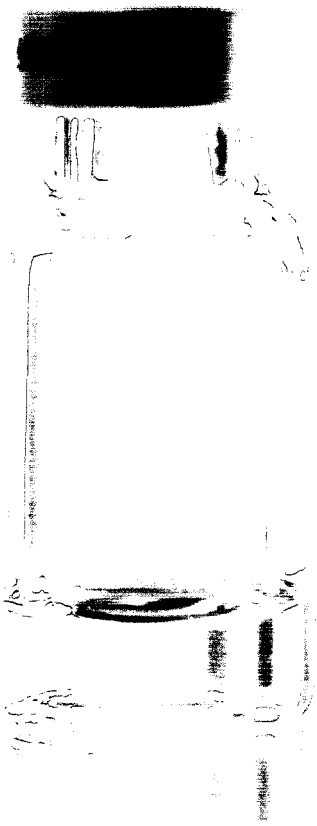
10.31.05 | 11.01.05 | 11.15.05 | 11.21.05 | 12.14.05 | 12.07.05 & 12.19.05

New RNAi Approach for *In Vivo* Therapeutic Silencing of microRNAs is Demonstrated by Alnylam and Rockefeller University Scientists and Published in *Nature*

microRNAs (miRNAs) are an exciting new discovery in the field of RNAi. Alnylam and Rockefeller University researchers published in *Nature* a novel approach to regulate gene expression through the silencing of miRNAs. The publication describes a potential new class of chemically modified RNA-based drugs, called "antagomirs," that specifically silence miRNAs. We believe that the opportunity to target miRNAs involved in human disease with antagomirs is an important extension of our platform to harness the RNAi pathway for discovery of innovative medicines.

Initiates Phase I Clinical Studies of ALN-RSV01 in U.S. and Europe for the Treatment of Respiratory Syncytial Virus (RSV) Infection

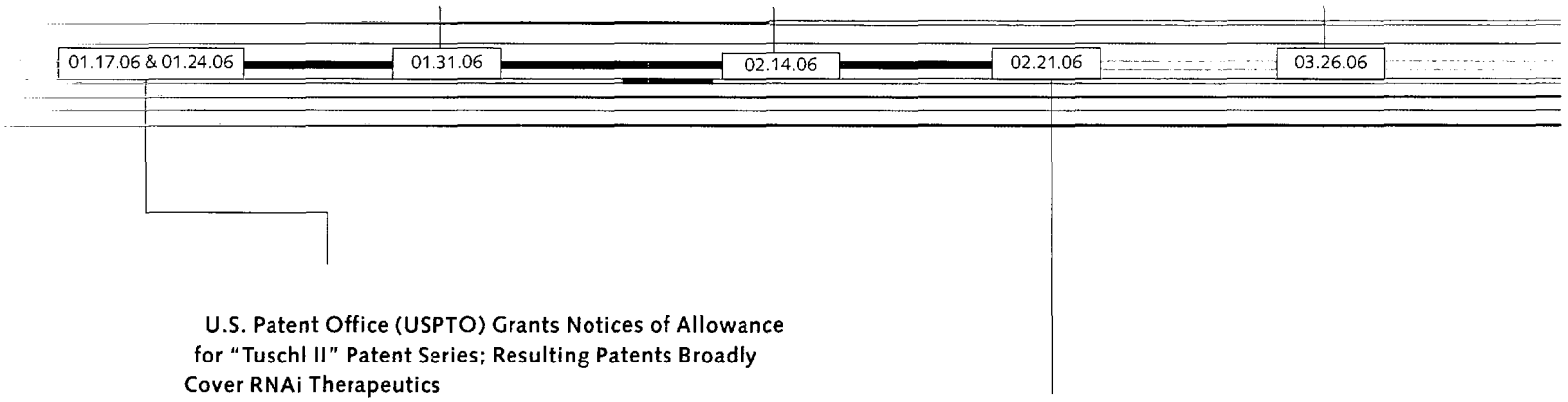
RSV infection is a serious medical issue for children and many adults and is the leading cause of infant hospitalization in the U.S. The lead product candidate in our clinical pipeline is ALN-RSV01, an RNAi therapeutic we are developing to treat RSV infection. In December 2005, we initiated two Phase I studies, in the U.S. and Europe, to evaluate the safety and pharmacology of ALN-RSV01 in healthy adult volunteers. Initiating these clinical trials was a major milestone for Alnylam and marked our transition to a clinical-stage company.



Completes Follow-on Public Offering Resulting in $66M in Gross Proceeds, Further Strengthening Balance Sheet

Awarded the James D. Watson Helix Award for Outstanding Corporate Achievement; Most Prestigious Honor in the Biotechnology Industry

New Data in Primates Representing Major Advancement for Systemic Delivery of RNAi Therapeutics Published in *Nature*



U.S. Patent Office (USPTO) Grants Notices of Allowance for "Tuschl II" Patent Series; Resulting Patents Broadly Cover RNAi Therapeutics

Alnylam's leading IP position was strengthened with the USPTO "Notices of Allowance" for patent applications 10/832,248 and 10/832,432 in the Tuschl II patent series covering methods for making siRNAs. The allowed claims of the Tuschl II patents broadly cover siRNA structure, function and use for therapeutic purposes. Based on the seminal research by Dr. Tuschl, a founder of Alnylam, this important patent series is exclusively licensed to Alnylam for RNAi therapeutics on a worldwide basis.

Novartis and Alnylam Form New Collaboration to Develop RNAi Therapeutics for Flu

The rapid spread of avian flu around the world increases the probability of a human pandemic, and strongly reinforces the need to discover and develop novel treatments for this serious public health threat. We believe that RNAi therapeutics can play a vital role in preparing for and responding to this threat, and could be used by governments across the world as part of strategic drug stockpiles. In the newly formed collaboration, Alnylam and Novartis will advance RNAi therapeutics for pandemic flu.

MARK FISHMAN, M.D.
President, Novartis Institutes for BioMedical Research

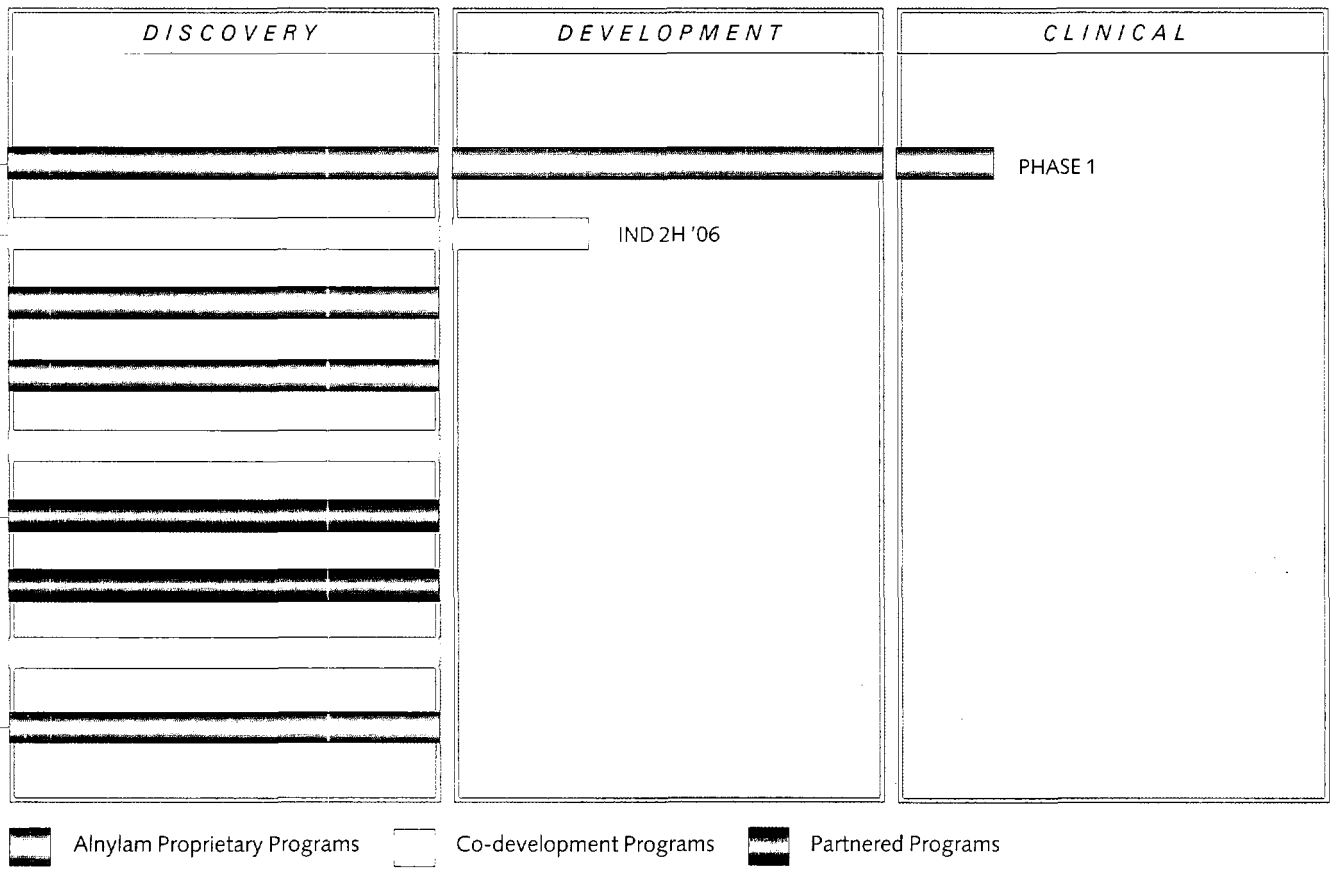
"Our two collaborations with Alnylam underscore Novartis' commitment to forging strategic alliances with partners at the forefront of scientific discovery. RNAi has potential to be a new therapeutic modality for treating many diseases, including diseases that cannot be addressed by traditional approaches. We look forward to continued progress with our combined efforts to develop innovative medicines to treat a broad range of therapeutic areas."

PRODUCT PIPELINE

- RSV infection
- Pandemic flu (w/ Novartis)
- Cystic fibrosis (w/ CF Foundation)
- Neuropathic pain
- NOGO pathway/spinal cord injury (w/ Merck)
- Parkinson's and Huntington's diseases (w/ Medtronic)
- Novartis programs
- Merck programs
- Alnylam pre-clinical programs

PHILLIP SHARP, PH.D.
Institute Professor, MIT Center for Cancer Research
Co-founder, Alnylam

"RNAi is the type of breakthrough discovery in biology that *happens only once every decade or so. The progress we have* made in developing RNAi therapeutics has been tremendous and has far exceeded my expectations. By harnessing a natural biological process in all of our cells, we have the potential to create an entirely new class of human therapeutics. I am excited by the high standards we have established in scientific leadership and *their recognition in world-class journals like Nature.*"



JOHN DeVINCENZO, M.D.
Associate Professor, Department of Pediatrics, University of Tennessee School of Medicine

"In my career, I have been committed to building a deep understanding of RSV and in developing strategies to control RSV infection. By utilizing RNAi for treatment, we have a unique opportunity to target lung infection due to RSV through a molecularly specific, natural, potent mechanism. Alnylam is addressing a significant unmet need to advance ALN-RSV01 for the treatment of RSV infection, a cause of serious disease and hospitalization in infants, the elderly, and others with compromised immune systems or chronic lung disease. Based on its novel mechanism of action and impressive pre-clinical efficacy data, ALN-RSV01 may represent a breakthrough treatment option for infected patients."

Alnylam's lead program is an RNAi therapeutic to treat respiratory syncytial virus infection, or RSV. RSV is a highly contagious virus that infects both the upper and lower respiratory tract affecting nearly every child by the age of two. RSV infection is a major cause of hospitalization in children and people with compromised immune systems and the leading cause of infant hospitalization in the U.S.

SCIENTIFIC AND PIPELINE LEADERSHIP

RSV infection typically results in cold-like symptoms but can lead to more serious respiratory illness such as croup, pneumonia, bronchiolitis, and in extreme cases, death. The development of childhood asthma is also believed to occur with increased frequency after serious RSV infection. There is a clear and significant need for novel therapeutics to treat patients infected with RSV.

The RNAi Opportunity: RNAi represents a significant opportunity in drug discovery today to create an entirely new class of drugs to treat human disease in a fundamentally new way.

RNAi is a naturally occurring mechanism within our cells for silencing genes. We are harnessing RNAi to selectively silence disease-causing genes. To create RNAi therapeutics we design and synthesize molecules known as siRNAs that are targeted to specific disease-associated genes. These siRNAs are delivered into cells and are used by the natural RNAi machinery inside cells to silence their target genes selectively. This ability to silence genes through RNAi provides the opportunity to develop a whole new class of innovative medicines to treat a broad range of human diseases.

Alnylam is a leading company in the field of RNAi therapeutics and we believe that the discovery of RNAi represents a discontinuity in biology similar to that which occurred in the 1970's with recombinant DNA and monoclonal antibody technology; it creates a very unique and exciting opportunity to create a new leading biopharmaceutical company.

BARRY E. GREENE
Chief Operating Officer

ROLAND KREUTZER, PH.D.
Managing Director,
Alnylam Europe AG

DAVID M. KONYS
Vice President, Corporate
Development and Operations

AKSHAY K. VAISHNAW, M.D., PH.D.
Vice President, Clinical Research

Product Strategy

Our product strategy is to build a pipeline of both Direct RNAi™ and Systemic RNAi™ therapeutics. For Direct RNAi, we administer RNAi therapeutics directly to sites of disease. This is the approach we have been pursuing to build our current pipeline of novel products. In parallel, we are developing Systemic RNAi applications, in which our drugs are administered by injection and travel through the bloodstream to reach diseased parts of the body. We believe there are a large number of opportunities for both Direct RNAi and Systemic RNAi therapeutics.

In addition, our strategy is to develop a pipeline with "multiple shots on goal" that allows us to increase the overall probability of building a sustainable pipeline of breakthrough marketed products. By focusing on new approaches for the treatment of disease, we are creating a pipeline that we believe will continue to be recognized by partners, and the healthcare system, for its innovative nature.

Finally, Alnylam is building a balanced pipeline of proprietary and partnered products. Our most advanced program, ALN-RSV01, remains a proprietary product. With Merck, Medtronic, and Novartis, we are developing a number of partnered programs.

RSV Program

Our most advanced product candidate is ALN-RSV01, a Direct RNAi therapeutic for the treatment of lung infections caused by RSV. We advanced this product candidate into Phase I human clinical studies in 2005, representing the first RNAi therapeutic for the treatment of a major infectious disease to enter clinical trials. RSV infection is the leading cause of pediatric hospitalizations in the U.S. and is also a major cause of infection in certain adult populations. While there are drugs on the market today to *prevent* RSV infection in high-risk premature infants, there are no effective drugs available to *treat* RSV infection, which is the need we are addressing. ALN-RSV01 is an RNAi therapeutic that has been shown to prevent and treat RSV replication in pre-clinical studies. We have initiated two Phase I studies of an intranasal formulation for this drug candidate, one in the U.S. and one in Europe. Results from these placebo-controlled studies are expected to provide us with a better understanding of the drug's safety and pharmacokinetic profile and prepare us for additional phases of human clinical testing.

Alnylam is developing RNAi therapeutics for pandemic flu. An influenza pandemic is a global outbreak of disease that occurs when a new, very infectious flu virus appears in the human population, causes serious illness, and spreads easily from person to person. Experts believe that current vaccines and existing anti-viral agents may not be sufficient to protect against newly emerging strains of influenza virus. Over the last several years, a highly virulent new strain of avian flu (H5N1) has become endemic in the poultry population in Southeast Asia, has spread to parts of Europe and Africa, and has caused significant mortality in humans that have been infected. The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) have expressed major concern about the potential for this virus to mutate into a form that could cause a global pandemic of human disease. Together with our partner Novartis, we aim to develop RNAi therapeutics to address this important global health concern.

Pandemic Flu

Given our successful efforts to date with our RSV program, we are also pursuing other respiratory viral infectious diseases – in particular, influenza. The threat of a global flu pandemic is a major concern for health authorities and governments worldwide. Experts agree that multiple approaches will be required to prepare for a pandemic. We believe that RNAi therapeutics can play a vital role in preparing for and responding to this threat. In fact, RNAi was specifically mentioned in the multi-billion dollar pandemic flu plan announced in 2005 by the U.S. Department of Health and Human Services. In our view, there is a significant opportunity to develop an RNAi therapeutic for pandemic flu that could be stockpiled by governments to prepare for a potential pandemic.

To develop such an RNAi therapeutic, we have created an important partnership between the private and public sectors. Our flu collaboration with Novartis dramatically expands our capabilities and global reach, and provides significant funding while preserving substantial downstream value for Alnylam through the sharing of profits.

Additional Programs

In addition to our development programs for RSV infection and pandemic flu, we have a number of pre-clinical programs, including proprietary programs for cystic fibrosis and neuropathic pain, and partnered programs for spinal cord injury, Parkinson's and Huntingon's diseases.

With our cystic fibrosis program, we are aiming to use RNAi to overcome the underlying genetic defect and restore normal lung function to patients afflicted with this disease. In our spinal cord injury program, our goal is to silence a key biological pathway that inhibits nerve regeneration after injury. For Parkinson's and Huntingon's diseases, we are combining cutting-edge device technologies to deliver our RNAi therapeutics to the central nervous system to create disease-modifying therapies which have not previously existed. For neuropathic pain, we can target a key gene involved in pain where other drugs have failed to achieve selectivity. Indeed, at the core of the RNAi opportunity, and Alnylam's strategy, is the ability to address human disease in a fundamentally new way.

VICTOR E. KOTELIANSKI, M.D., PH.D.
Vice President, Research

MUTHIAH MANOHARAN, PH.D.
Vice President, Drug Discovery

HANS-PETER VORNLOCHER, PH.D.
Managing Director, Research, Alnylam Europe AG

NAGESH MAHANTHAPPA, PH.D.
Senior Director, Business Development and Strategy

Scientific Leadership

Throughout 2005 and into early 2006, researchers at Alnylam continued to advance RNAi technology and to lead in translating this ground-breaking scientific discovery into innovative medicines. We have made very significant progress toward development of Systemic RNAi therapeutics, including improvements in the potency and efficacy of systemically administered siRNAs in animal models of human disease. Most recently, we published in one of the world's leading journals, *Nature*, the first-ever demonstration in primates of an RNAi therapeutic silencing a disease-causing gene. We targeted a gene involved in cholesterol metabolism and, in animal models, our siRNA exceeded the therapeutic efficacy achieved with cholesterol lowering drugs on the market today.

As a leader in the field of RNAi, we are also at the forefront in the emerging science of microRNAs, or miRNAs. These are small RNAs that exist naturally within mammalian cells and appear to regulate gene activity through the RNAi pathway. miRNAs have been shown to regulate a large number of genes in the human genome and have been clearly implicated in cancer, viral infections, and other diseases. Alnylam scientists and collaborators invented antagomirs, a class of chemically modified RNAs that are designed to specifically silence miRNAs in human disease. These findings were also published in the peer-reviewed journal, *Nature*. We believe this major advance in the RNAi field will be an important future area for Alnylam.

Alnylam is the 2006 recipient of the biotechnology industry's prestigious James D. Watson Helix award in the "emerging/mid-cap" category. The Helix award, the biotechnology industry's award for outstanding corporate achievement, honors biotechnology companies that display leadership in three distinct areas:

INTELLECTUAL PROPERTY AND BUSINESS LEADERSHIP

product development, economic growth, and corporate citizenship. It is a distinct honor to be recognized for our bold vision to harness RNAi to create a whole new class of innovative medicines and for executing on our mission to build a leading biopharmaceutical company.

2005 was a year of strong and rapid progress for Alnylam. In addition to becoming a clinical-stage company, we entered into substantial innovation-based collaborations with major pharmaceutical companies, maintained a strong financial profile, and strengthened and leveraged our intellectual property estate.

Intellectual property (IP) has been a cornerstone of our business strategy from the earliest days of the company, and we have established what we believe to be an unrivaled position in IP that will be necessary for the discovery, development, and commercialization of RNAi therapeutics. This includes "fundamental" IP relating to the key properties of siRNAs and their use as therapeutics, as well as IP relating to chemistry and targets. To our knowledge, Alnylam and its licensees are the only companies that currently have access to all fundamental RNAi patents issued or granted in major markets that are needed to commercialize RNAi therapeutics. Our IP position is enabling Alnylam to maximize value from the development of RNAi therapeutics as a whole new class of drugs. The strength of this position is clearly recognized by others, resulting in our ability to successfully forge over 20 significant relationships over the last three years that involve our IP. We expect to continue this track record of execution in 2006.

VINCENT J. MILES, PH.D.
Senior Vice President,
Business Development

PATRICIA L. ALLEN
Vice President, Finance
and Treasurer

ANDREAS BOSSKO
Managing Director, Finance,
Alnylam Europe AG

ROBERT MILLMAN
Chief Intellectual
Property Counsel

These relationships are the product of an active corporate partnering and licensing strategy that has been very successful in taking advantage of our leading scientific and IP positions to build value and grow our business. Key components of this strategy include: forging major alliances with biopharmaceutical companies to develop RNAi therapeutics; further consolidating our IP position through agreements with other companies; providing licenses under our IP to other biotechnology companies focused on RNAi therapeutics outside our own areas of strategic interest, or on research reagents; and securing funding from major foundations and government agencies.

In 2005, we signed our most important alliance to date – a major alliance with Novartis, a leading global biopharmaceutical company, that we believe is one of the most significant innovation-based drug discovery alliances in the biotechnology industry. Success in this alliance could provide us with over $700 million in funding that includes $68.5 million in upfront payments already made by Novartis. Importantly, this collaboration also allows us to continue to develop our own proprietary pipeline of RNAi therapeutics. In early 2006, we entered into a second distinct collaboration with Novartis, focused on developing RNAi therapeutics for pandemic flu. This new collaboration provides significant funding while preserving substantial downstream value for Alnylam through the sharing of profits.

All told, we currently have five distinct collaborations with three major pharmaceutical companies. Clearly, leading healthcare companies have recognized the therapeutic potential for RNAi and the significant scientific and IP leadership at Alnylam. In addition to the two partnerships with Novartis, we have an alliance with Merck to jointly develop RNAi therapeutics for up to 12 disease targets, another with Merck focused on ocular disease, and an alliance with Medtronic in which we are working together to develop novel drug-device products that combine RNAi therapeutics with implantable infusion pump technology for the treatment of major neurodegenerative diseases. Our alliances have provided us with cash funding of over $100 million to date, and we expect they will continue to provide significant future funding in the form of research and development support, milestone payments, potential additional equity investments, and royalties and/or share of profits.

Officers and Senior Management

John M. Maraganore, Ph.D.
President and Chief Executive Officer

Barry E. Greene
Chief Operating Officer

Patricia L. Allen
Vice President, Finance and Treasurer

Andreas Bossko
Managing Director, Finance, Alnylam Europe AG

David M. Konys
Vice President, Corporate Development and Operations

Victor E. Kotelianski, M.D., Ph.D.
Vice President, Research

Roland Kreutzer, Ph.D.
Managing Director, Alnylam Europe AG

Muthiah Manoharan, Ph.D.
Vice President, Drug Discovery

Nagesh Mahanthappa, Ph.D.
Senior Director, Business Development and Strategy

Vincent J. Miles, Ph.D.
Senior Vice President, Business Development

Robert Millman
Chief Intellectual Property Counsel

Akshay K. Vaishnaw, M.D., Ph.D.
Vice President, Clinical Research

Hans-Peter Vornlocher, Ph.D.
Managing Director, Research, Alnylam Europe AG

Board of Directors

Peter Barrett, Ph.D.
Senior Principal, Atlas Venture

John K. Clarke
Managing General Partner, Cardinal Partners
Chairman of the Board, Alnylam Pharmaceuticals, Inc.

John M. Maraganore, Ph.D.
President and Chief Executive Officer, Alnylam Pharmaceuticals, Inc.

Vicki L. Sato, Ph.D.
Former President of Vertex Pharmaceuticals Incorporated

Phillip A. Sharp, Ph.D.
Institute Professor, Massachusetts Institute of Technology
Nobel Laureate in Physiology or Medicine, 1993

Paul R. Schimmel, Ph.D.
Skaggs Institute for Chemical Biology,
The Scripps Research Institute

Kevin P. Starr
Former Chief Operating Officer, Millennium Pharmaceuticals, Inc.

James L. Vincent, Ph.D.
Former Chairman and CEO of Biogen, Inc. (now BiogenIdec, Inc.)

Stockholder Information

Corporate Headquarters

Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, Massachusetts 02142
617.551.8200

Independent Auditors

PricewaterhouseCoopers LLP, Boston, Massachusetts

Transfer Agent and Registrar

Questions regarding accounts, address changes,
stock transfers and lost certificates should be directed to:
Computershare (formerly EquiServe)
P.O. Box 43023
Providence, Rhode Island 02940-3023
Shareholder Inquiries 781.575.2879
www.computershare.com

Annual Meeting

The 2006 Annual Meeting of Stockholders will be held on June 1, 2006 at 9:00 a.m. at the offices of Alnylam Pharmaceuticals, Inc., 300 Third Street, Cambridge, Massachusetts.

Price Range of Common Stock

Alnylam's common stock began trading on the NASDAQ National Market on May 28, 2004 under the symbol ALNY. Prior to that time there was no established public trading market for our common stock. The following table sets forth the high and low sales prices per share for our common stock on the NASDAQ National Market for the periods indicated:

	2005		2004	
	High	Low	High	Low
First Quarter	$11.00	$6.76	–	–
Second Quarter (beginning May 28, 2004)	9.00	6.90	$9.50	$5.26
Third Quarter	15.22	6.90	8.00	3.65
Fourth Quarter	14.85	9.06	8.60	5.00

No dividends have been paid on the common stock to date and the company does not expect to pay cash dividends on such common stock in the foreseeable future.

SEC Form 10-K

A copy of the company's Form 10-K for the year ended December 31, 2005, filed with the Securities and Exchange Commission is available without charge upon written request to:

Investor Relations
Attention: Cynthia Clayton
Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, Massachusetts 02142
www.alnylam.com

This document contains forward-looking statements that involve risks and uncertainties. Any statements (including statements to the effect that we "believe" and similar expressions) that are not statements relating to historical matters should be considered forward-looking statements. Actual results may differ materially from those discussed in the forward-looking statements as a result of numerous important factors, including those discussed in "Risk Factors" in our Annual Report on Form 10-K.

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